Insect Repellency of Substituted *N,N*-Diethylbenzamidines

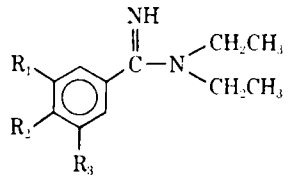
DANIEL D. GARNER* and LORRIN R. GARSON▲

Abstract □ The synthesis of *N,N*-diethylbenzamidine, *N,N*-diethyl-3-trifluoromethylbenzamidine, *N,N*-diethyl-4-trifluoromethylbenzamidine, and *N,N*-diethyl-3,5-di(trifluoromethyl)benzamidine is described; the compounds were designed to produce long-lasting insect repellent activity. The repellency of these agents on cloth against *Aedes aegypti* (L.) mosquitoes is reported.

Keyphrases □ *N,N*-Diethylbenzamidines, substituted—synthesized and evaluated as potential insect repellents □ Insect repellents, potential—synthesis and evaluation of substituted *N,N*-diethylbenzamidines □ Repellents, insect—synthesis and evaluation of substituted *N,N*-diethylbenzamidines

Associated with efforts to develop long-lasting insect repellents and prompted by the remarkable efficacy elicited by *N,N*-diethyl-*m*-toluamidine (I) (1), four additional amidines were synthesized and evaluated as repellents. Although Compound I exhibited a higher degree of repellency than the standard repellent 2-ethyl-1,3-hexanediol[1], a drying action on the skin of some volunteers was produced by this agent. Since this adverse effect may have been a manifestation of the strong basicity of I, the design of III–V included structural features to effect reduced basicity.

Volatility has long been associated with insect repellent activity (2); the lower activity of I compared to *N,N*-diethyl-*m*-toluamide could be due to the latter's higher volatility as indicated by the boiling points [*i.e.*, *N,N*-diethyl-*m*-toluamide, b.p. 111°/1.0 mm. (3); I, b.p. 148°/1.0 mm. (1)]. An inverse linear relationship was shown (4) between insect repellency and boiling point for ring-substituted *N,N*-diethylbenzamides. By assuming that this relationship is also applicable to the corresponding amidine series, II–IV were designed to obtain an agent with the optimal volatility associated with maximum effectiveness as a repellent. Also of significance is the fact that II is a nitrogen isostere of *N,N*-diethylbenzamide, an excellent repellent (5).



Compound	R_1	R_2	R_3
I	H	H	CH_3
II	H	H	H
III	H	H	CF_3
IV	H	CF_3	H
V	CF_3	H	CF_3

EXPERIMENTAL[2]

***N,N*-Diethylbenzamidine (II)**—By employing the method described for the preparation of I (1), 24.9 g. (0.540 mole) of absolute ethanol, 75 ml. of anhydrous ether, and 44.0 g. (0.427 mole) of benzonitrile were combined and cooled to −7°. After the addition of 37.8 g. (1.04 moles) of hydrogen chloride, the reaction mixture was stirred for 14 hr. Ethyl benzimidate hydrochloride (VI) was collected by filtration, washed with ether, and dried *in vacuo* for 2 hr., yielding 53.7 g. (67.7%). The hydrochloride (0.289 mole) was allowed to stand for 1 week with 63.2 g. (0.864 mole) of diethylamine in 200 ml. of absolute ethanol. Then the reaction mixture was distilled *in vacuo*, leaving a dark-brown residual liquid.

The crude material was dissolved in 500 ml. of 10% sodium bicarbonate and divided into two portions, and each was extracted with ether (4 × 50 ml.). The aqueous phase was brought to a higher pH (pH 11–13) by adding sodium hydroxide until a second layer appeared, at which time the basic solution was extracted with ether (4 × 100 ml.). The ether solutions from the second extraction were combined, dried over magnesium sulfate, and filtered; the ether was removed by distillation *in vacuo*, yielding a yellow residual liquid. The crude product was purified by distillation *in vacuo*, employing a short-path, microdistillation apparatus, yielding 20.7 g. (40.6%) of pure II, b.p. 62–63° (0.2 mm.); n_D^{25} 1.5322; IR (chloroform): 1575 cm.$^{-1}$ (C=N); UV (95% ethanol): 205 nm. (ε 14,100).

Anal.—Calc. for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.07; H, 9.17; N, 15.81.

***N,N*-Diethyl-3-trifluoromethylbenzamidine (III)**—Ethyl 3-trifluoromethylbenzimidate hydrochloride was prepared in an analogous manner to VI, using 14.6 g. (0.317 mole) of absolute ethanol, 43.0 g. (0.251 mole) of *m*-trifluoromethylbenzonitrile, and 18.3 g. (0.502 mole) of hydrogen chloride, yielding 49.5 g. (77.7%) of the salt. The salt was allowed to react in a similar manner as described in the preparation of II, using 42.8 g. (0.585 mole) of diethylamine. The product was purified by distillation *in vacuo*, yielding 19.4 g. (40.8%) of colorless III, b.p. 66–68° (0.1–0.2 mm.); n_D^{25} 1.4814; IR (chloroform): 1572 cm.$^{-1}$ (C=N); UV (95% ethanol): 205 nm. (ε 14,500).

Anal.—Calc. for $C_{12}H_{15}F_3N_2$: C, 59.01; H, 6.19; F, 23.34; N, 11.47. Found: C, 59.22; H, 6.16; F, 23.23; N, 11.46.

***N,N*-Diethyl-4-trifluoromethylbenzamidine (IV)**—Ethyl 4-trifluoromethylbenzimidate hydrochloride was prepared in a similar manner to VI, using 17.0 g. (0.369 mole) of absolute ethanol, 50.0 g. (0.292 mole) of *p*-trifluoromethylbenzonitrile, and 23.5 g. (0.644 mole) of hydrogen chloride, yielding 65.4 g. (88.3%) of the benzimidate salt. Compound IV was prepared using 56.6 g. (0.774 mole) of diethylamine and the salt. The product was distilled *in vacuo*, yielding 23.6 g. (37.5%) of yellow-colored IV, b.p. 74–76° (0.05 mm.); n_D^{25}/1.4824; IR (chloroform): 1580 cm.$^{-1}$ (C=N); UV (95% ethanol): 208 nm. (ε 13,700).

Anal.—Calc. for $C_{12}H_{15}F_3N_2$: C, 59.01; H, 6.19; F, 23.34; N, 11.47. Found: C, 58.95; H, 6.24; F, 23.52; N, 11.41.

***N,N*-Diethyl-3,5-di(trifluoromethyl)benzamidine (V)**—In a comparable manner to VI, ethyl 3,5-di(trifluoromethyl)benzimidate hydrochloride was prepared using 12.1 g. (0.263 mole) of absolute ethanol, 50.0 g. (0.209 mole) of 3,5-di(trifluoromethyl)benzonitrile, and 15.0 g. (0.411 mole) of hydrogen chloride, yielding 66.1 g. (98.4%) of the salt. A mixture of 66.1 g. (0.205 mole) of the benzimidate salt, 200 ml. of isopropyl alcohol, and 46.5 g. (0.636 mole) of diethylamine was stirred at 75° for 5 days. Then the mixture was distilled *in vacuo*, leaving a red residual solid.

The crude material was shaken with water buffered at pH 7, the undissolved material was removed, and the aqueous phase was extracted with ether (3 × 100 ml.). The insoluble material was dissolved in 500 ml. of an aqueous sodium hydroxide solution (pH 12) and, after the appearance of a second layer following the addition of more sodium hydroxide, the basic solution was extracted with

[1] Rutgers 612.

[2] Boiling points are uncorrected. IR and UV spectra were obtained with the Perkin-Elmer models 137B and 202 spectrophotometers, respectively. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

ether (3 × 100 ml.). The ether solutions from the second extraction were combined, dried over magnesium sulfate, and filtered, and the ether was removed by distillation *in vacuo*, yielding a purple residual liquid. The crude product was purified by distillation *in vacuo*, employing a microdistillation apparatus (24-cm. Vigreux column), yielding 10.9 g. (17.0%) of pure V, b.p. 60 65° (0.01–0.02 mm.); n_D^{25} 1.4465; IR (chloroform): 1580 cm.$^{-1}$ (C=N); UV (95% ethanol): 208 nm. (ϵ 15,000).

Anal.—Calc. for $C_{13}H_{14}F_6N_2$: C, 50.00; H, 4.52; F, 36.51; N, 8.97. Found: C, 50.07; H, 4.57; F, 36.23; N, 8.76.

Evaluation of Repellency—To minimize contact with the skin, Compounds II–V were evaluated as repellents against *Aedes aegypti* (L.) mosquitoes employing a standard cloth method (6); *N,N*-diethyl-*m*-toluamide was included in the tests as a standard for comparison. One-third square foot of a cotton stocking was treated with 1 g. of the compound in solution (10% solution in a volatile solvent, usually acetone). Two hours after treatment, the stocking, on the arm of a human subject, was exposed for 1 min. in a cage of mosquitoes. If less than five mosquitoes bit the subject through the stocking, the test was repeated at 24 hr. and then weekly thereafter until five bites were received in 1 min.

RESULTS AND DISCUSSION

As tested, Compounds II–V were found to be effective on cloth against *Aedes aegypti* (L.) mosquitoes for 7 days as compared to *N,N*-diethyl-*m*-toluamide and *N,N*-diethylbenzamide, which are effective under the same conditions for more than 21 days. To our knowledge, Compounds I–V are the only amidines that have been evaluated as insect repellents. The effectiveness of these specific agents and the structural similarities between amidines and amides and imides, which were found (7) to be the largest single class of compounds effective for 5 hr. or more upon dermal application, indicate that amidines as a class possess considerable potential as insectifugal agents.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 15, 1973, from the *Department of Medicina Chemistry, College of Pharmacy, University of Tennessee Medical Units, Memphis, TN 38103*

Accepted for publication July 19, 1973.

Abstracted in part from a dissertation to be submitted by D. D. Garner to the University of Tennessee in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported by Research Contract DA-49-193-MD-2636 from the U. S. Army Medical Research and Development Command, Washington, D. C.

The authors gratefully acknowledge the assistance of Dr. D. E. Weidhaas, Mr. I. H. Gilbert, and their colleagues of the Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Gainesville, Fla., in the evaluation of mosquito repellency.

• American Foundation for Pharmaceutical Education Fellow, 1972–1973.

▲ To whom inquiries should be directed.

Metabolism and Anticonvulsant Activity of Deuterated *N*-Demethyldiazepam

FRANCA MARCUCCI, EMILIO MUSSINI, PAOLA MARTELLI, AMALIA GUAITANI, and SILVIO GARATTINI▲

Abstract □ The substitution of the hydrogen at the C_3-position of *N*-demethyldiazepam with deuterium shortens the anticonvulsant activity in mice from 20 to 5 hr. This pharmacological effect may be partly explained by a decrease in the ability of deuterated *N*-demethyldiazepam to protect mice from pentylenetetrazol-induced convulsions in contrast to the effect exerted by the C_3-unlabeled analog. Furthermore, the weaker pharmacological action of deuterated *N*-demethyldiazepam may in part be due to the lesser accumulation of the hydroxylated metabolite, oxazepam, in the brain of mice treated with deuterated *N*-demethyldiazepam than with the unlabeled analog. The lesser accumulation of oxazepam from deuterated *N*-demethyldiazepam than from the unlabeled analog is due to a reduced C_3-hydroxylation of this compound by liver microsomal enzymes, as shown by experiments *in vitro*.

Keyphrases □ Diazepam, *N*-demethyl, deuterated—metabolism and anticonvulsant activity, mice □ *N*-Demethyldiazepam, deuterated—metabolism and anticonvulsant activity, mice □ Anticonvulsant activity—deuterated *N*-demethyldiazepam, metabolism, mice □ Oxazepam—accumulation after administration of deuterated *N*-demethyldiazepam, mice

N-Demethyldiazepam, a major metabolite of diazepam, possesses pharmacological properties similar to the parent compound (1, 2). In the liver microsomal system, it undergoes a process of hydroxylation in position C_3 with the formation of oxazepam (3). The administration of *N*-demethyldiazepam in mice results in an accumulation of oxazepam in brain (4) where it is retained for several hours. Because oxazepam exerts