(3) J. T. Ingram, *Br. Med. J.*, **2**, 591 (1953).
(4) S. Comaish, *Arch. Dermatol.*, **92**, 26 (1965).
(5) R. H. Seville, *Br. J. Dermatol.*, **78**, 269 (1966).
(6) E. Young, *ibid.*, **82**, 516 (1970).
(7) W. P. Raab and B. M. Gmeiner, *Dermatologica*, **150**, 267 (1975).
(8) H. J. Hulsebosch and M. Ponec-Waelsch, *ibid.*, **144**, 287 (1972).
(9) M. Ponec-Waelsch and H. J. Hulsebosch, *Arch. Dermatol. Forsch.*, **249**, 141 (1974).
(10) S. Comaish, J. Smith, and R. H. Seville, *Br. J. Dermatol.*, **84**, 282 (1971).
(11) P. Arends, *J. Chromatogr.*, **47**, 550 (1970).
(12) H. Beerman, G. V. Kulchar, and D. M. Pillsbury, *J. Am. Med. Assoc.*, **104**, 26 (1935).
(13) E. M. Farber and D. R. Harris, *Arch. Dermatol.*, **101**, 381 (1970).
(14) M. W. Gay, W. J. Moore, J. M. Morgan, and L. F. Montes, *ibid.*, **105**, 213 (1972).
(15) H. Baker and T. J. Ryan, *Br. J. Dermatol.*, **80**, 771 (1968).
(16) M. Whitefield, *Arzneim.-Forsch.*, **20**, 137 (1970).
(17) A. Segal, C. Kutz, and B. L. Van Duuren, *J. Med. Chem.*, **14**, 394 (1971).
(18) H. Thielemann, *Sci. Pharm.*, **42**, 55 (1974).
(19) E. G. Clarke, "Isolation and Identification of Drugs," vol. 2, Pharmaceutical Press, London, England, 1975, p. 1025.
(20) "The Merck Index," 9th ed., Merck and Co., Rahway, N.J., 1976, p. 3394.
(21) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 33.

ACKNOWLEDGMENTS

The authors thank Ms. Yanee Pongpaibul for technical assistance.

Topical Mosquito Repellents XI: Carbamates Derived from *N,N'*-Disubstituted Diamines

W. A. SKINNER ˣ, H. T. CRAWFORD, L. C. RUTLEDGE *, and M. A. MOUSSA ‡

Received May 26, 1978, from the *Life Sciences Division, SRI International, Menlo Park, CA 94025.* Accepted for publication August 17, 1978. *Present address: Letterman Army Institute of Research, Presidio of San Francisco, CA 94129. ‡Present address: Medical Entomology Consultant, Office of the Surgeon General, Washington, DC 20310.

Abstract □ Carbamates derived from various *N,N'*-disubstituted diamines were synthesized and evaluated as repellents for *Aedes aegypti* mosquitoes with an *in vitro* blood-feeding test system. Several compounds were more effective than diethyltoluamide.

Keyphrases □ Carbamates from *N,N'*-disubstituted amines—synthesized and evaluated as mosquito repellents □ Repellents, mosquito—various carbamates derived from *N,N'*-disubstituted diamines synthesized and evaluated □ Structure–activity relationships—various carbamates derived from *N,N'*-disubstituted diamines evaluated as mosquito repellents

Carbamates as mosquito repellents were discussed previously (1). Substituted 2-oxazolidones were synthesized and found to possess repellent activity (1). However, improvement of their repellency was desired, and a new synthetic effort was initiated to prepare carbamates from *N,N'*-disubstituted diamines.

To vary the boiling-point ranges of the proposed repellents, syntheses were concentrated on ethylenediamine, diethylenediamine, and triethylenediamine derivatives. Previous studies (1) showed that repellency duration is a function of boiling points or volatility of repellents.

These compounds were evaluated in the *in vitro* mosquito blood-feeding test system reported previously (2). Mosquitoes used for these evaluations were female *Aedes aegypti* (yellow fever mosquito).

Table I—Physical and Biological Properties of Carbamates Derived from *N,N'*-Disubstituted Diamines

$R_1N(CH_2CH_2)_nNR_3$ (R_2, R_4)

Compound	R_1	R_2	R_3	R_4	n	Boiling Point (0.5 mm Hg)	Repellency ED_{50}	Repellency ED_{90}	r
I[a]	C_3H_7	H	C_3H_7	CO_2CH_3	1	90°	2.8	79	−0.97
II[b]	C_4H_9	H	C_4H_9	CO_2CH_3	1	102°	0.12	0.59	−0.88
III[c]	C_3H_7	CO_2CH_3	C_3H_7	CO_2CH_3	1	110°	0.049	0.13	−0.92
IV[b]	C_4H_9	CO_2CH_3	C_4H_9	CO_2CH_3	1	130°	0.014	0.072	−0.87
V[d]	C_6H_{13}	H	C_6H_{13}	CO_2CH_3	1	146°	0.028	0.083	−0.79
VI[e]	C_6H_{13}	CO_2CH_3	C_6H_{13}	CO_2CH_3	1	160°	0.036	0.21	−0.84
VII[f]	C_3H_7	H	C_3H_7	CO_2CH_3	2	112°	0.25	2.5	−0.68
VIII[g]	C_3H_7	CO_2CH_3	C_3H_7	CO_2CH_3	2	141°	0.020	0.073	−0.96
IX[h]	C_3H_7	H	C_3H_7	CO_2CH_3	3	131°	0.23	4.0	−0.68
X[i]	C_3H_7	CO_2CH_3	C_3H_7	CO_2CH_3	3	155°	0.018	0.10	−0.82
Diethyltoluamide						100°	0.031	0.10	−0.81
N,N'-Dihexamethylenecarbamide						130°	0.00081	0.056	−0.83

[a] *Anal.*—Calc. for $C_{10}H_{22}N_2O$: C, 59.37; H, 10.98; N, 13.85. Found: C, 58.84; H, 11.03; N, 13.76. [b] See *Experimental.* [c] *Anal.*—Calc. for $C_{12}H_{24}N_2O_4$: C, 55.36; H, 9.29; N, 10.76. Found: C, 55.15; H, 9.23; N, 10.70. [d] *Anal.*—Calc. for $C_{16}H_{34}N_2O_2$: C, 67.08; H, 11.96; N, 9.78. Found: C, 66.99; H, 11.87; N, 9.66. [e] *Anal.*—Calc. for $C_{18}H_{36}N_2O_4$: C, 62.75; H, 10.53; N, 8.13. Found: C, 63.05; H, 10.74; N, 8.23. [f] *Anal.*—Calc. for $C_{12}H_{26}N_2O_2$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.44; H, 11.54; N, 12.05. [g] *Anal.*—Calc. for $C_{14}H_{28}N_2O_4$: C, 58.30; H, 9.79; N, 9.72. Found: C, 57.99; H, 9.85; N, 9.68. [h] *Anal.*—Calc. for $C_{14}H_{30}N_2O_2$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.07; H, 11.74; N, 10.66. [i] *Anal.*—Calc. for $C_{16}H_{32}N_2O_4$: C, 60.73; H, 10.19; N, 8.85. Found: C, 60.65; H, 10.39; N, 8.66.

0022-3549/79/0300-0390$01.00/0

EXPERIMENTAL[1]

To prepare *N,N'*-dibutyl-*N*-methoxycarbonylethylenediamine (II) and *N,N'*-dibutyl-*N,N'*-di(methoxycarbonyl)ethylenediamine (IV), a 1-liter, three-necked flask was fitted with a thermometer, an addition funnel, a magnetic stirrer, a reflux condenser, and a heating mantle. The diamine (25 g, 0.145 mole) was dissolved in anhydrous methanol (800 ml) and placed in the flask. As this solution was slowly heated to 60°, a solution of methyl chloroformate (13.7 g, 0.145 mole) in anhydrous methanol (50 ml) was added dropwise over 1 hr. The reaction mixture was stirred at 60° for an additional 3 hr and then overnight at room temperature.

The methanol was removed *in vacuo*, and the residue was taken up in methylene chloride (300 ml), filtered to remove the hydrochloride salt of the starting material, and concentrated *in vacuo*. The residue was dissolved in distilled water, acidified (pH 3), and extracted with ether (three times) to yield Fraction E_1. The aqueous solution was made basic with 10% NaOH and reextracted with ether (three times), affording Fraction E_2.

Distillation of E_1 yielded 12.1 g of IV, bp 123°/0.35 mm Hg.

Anal.—Calc. for $C_{14}H_{28}N_2O_4$: C, 58.31; H, 9.79; N, 9.72. Found: C, 58.17; H, 9.92; N, 9.69.

Fraction E_2 was dried, evaporated *in vacuo*, and distilled to yield 17.1 g of II, bp 96–98°/0.4 mm Hg.

Anal.—Calc. for $C_{12}H_{26}N_2O_2$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.25; H, 11.43; N, 12.09.

[1] Boiling points were determined using a short path distillation apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, Stanford University, Stanford, Calif.

RESULTS AND DISCUSSION

Table I gives the structures, boiling points, and repellency data of the tested carbamates.

Compounds IV–VI, VIII, and X had ED_{50} values equal to or less than that of diethyltoluamide. The ED_{90} values of III–V, VII, and X were outstanding. These values indicate that all of these compounds should be considered as candidate repellents to replace diethyltoluamide, and advanced repellency and preliminary toxicity tests are planned.

With these compounds, the boiling range for effective repellency in this test system is considerably higher that of diethyltoluamide (100°/0.5 mm Hg), being 110–160°/0.5 mm Hg. These less volatile repellents may have an increased duration of effectiveness when applied to human skin.

Future studies will depend on the results of human skin tests of the best compounds of the series.

REFERENCES

(1) W. A. Skinner, H. T. Crawford, D. Skidmore, and H. I. Maibach, *J. Pharm. Sci.*, **66**, 587 (1977).

(2) L. C. Rutledge, M. A. Moussa, and C. J. Belletti, *Mosquito News*, **36**, 283 (1976).

ACKNOWLEDGMENTS

Supported by U.S. Army Medical Research and Development Command Contract DADA 17-70-C-0112.

Topical Mosquito Repellents XII: *N*-Substituted Ureas and Cyclic Ureas

W. A. SKINNER ˣ, H. T. CRAWFORD, L. C. RUTLEDGE *, and M. A. MOUSSA ‡

Received June 5, 1978, from the *Life Sciences Division, SRI International, Menlo Park, CA 94025.* Accepted for publication August 17, 1978. *Present address: Letterman Army Institute of Research, Presidio of San Francisco, CA 94129. ‡Present address: Medical Entomology Consultant, Office of the Surgeon General, Washington, DC 20310.

Abstract □ Various *N*-substituted urea and cyclic urea derivatives were synthesized and evaluated as repellents for *Aedes aegypti* mosquitoes with an *in vitro* blood-feeding test system. Several compounds were superior to diethyltoluamide.

Keyphrases ◻ Ureas and cyclic ureas, *N*-substituted—synthesized and evaluated as mosquito repellents □ Repellents, mosquito—various *N*-substituted ureas and cyclic ureas synthesized and evaluated □ Structure–activity relationships—various *N*-substituted ureas and cyclic ureas evaluated as mosquito repellents

In continuing efforts to find improved mosquito repellents, various *N*-substituted ureas and cyclic ureas were synthesized for evaluation in an *in vitro* blood-feeding test system using *Aedes aegypti* mosquitoes as described previously (1).

N,N'-Dihexamethylenecarbamide[1], a urea derivative, was reported (2) to be effective as a repellent for mosquitoes and black flies. The minimum effective dosage was 0.04 mg/cm^2 for mosquitoes (*A. hexodontus* and *A. punctor*) and 0.12 mg/cm^2 for black flies (*Simulium venustum*) when evaluated on human skin. The minimum effective dosages obtained for *N,N'*-dihexamethylenecarbamide were lower than those for diethyltoluamide (0.14 mg/cm^2) for the same mosquitoes.

In view of the interesting effectiveness of this *N*-substituted urea, it was decided to explore the structure–repellent activity relationships of *N*-substituted ureas and cyclic ureas. To vary the boiling-point ranges, both open chain and cyclic ureas were synthesized. For the same reason, substituents on the nitrogens were varied in alkyl chain lengths.

EXPERIMENTAL[2]

Preparation of *N,N'*-Dibutylurea (IV)—A 1-liter, three-necked flask was charged with 200 ml of benzene, and phosgene was bubbled

[1] Carboxide.

[2] Boiling points were determined using a short path distillation apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, Stanford University, Stanford, Calif.

0022-3549/79/0300-0391$01.00/0