

EXPERIMENTAL¹

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 E₁. The aqueous solution was made basic with 10% NaOH and reextracted with ether (three times), affording Fraction E₂.

Distillation of E₁ yielded 12.1 g of IV, bp 123°/0.35 mm Hg.

Anal.—Calc. for C₁₄H₂₈N₂O₄: C, 58.31; H, 9.79; N, 9.72. Found: C, 58.17; H, 9.92; N, 9.69.

Fraction E₂ was dried, evaporated *in vacuo*, and distilled to yield 17.1 g of II, bp 96–98°/0.4 mm Hg.

Anal.—Calc. for C₁₂H₂₆N₂O₂: C, 62.57; H, 11.38; N, 12.16. Found: C,

62.25; H, 11.43; N, 12.09.

RESULTS AND DISCUSSION

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

Compounds IV–VI, VIII, and X had ED₅₀ values equal to or less than that of diethyltoluamide. The ED₉₀ 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 than 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

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ACKNOWLEDGMENTS

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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.

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

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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'-Dihexamethylenecarbamide¹, 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/cm² for mosquitoes (*A. hexodontus* and *A. punctator*) and 0.12 mg/cm² 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/cm²) 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.

EXPERIMENTAL²

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

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.

¹ Carbamide.

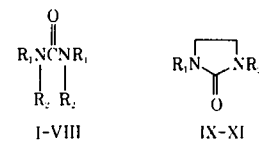


Table I—Physical and Biological Properties of *N*-Substituted Ureas and Cyclic Ureas

| Compound | R ₁ | R ₂ | Boiling Point (0.5 mm Hg) | Repellency | | |
|---------------------------------------|--------------------------------|-----------------------------------|------------------------------|------------------|------------------|----------|
| | | | | ED ₅₀ | ED ₉₀ | <i>r</i> |
| I ^a | C ₃ H ₇ | C ₃ H ₇ | 81° | 0.075 | 0.25 | -0.92 |
| II ^b | C ₄ H ₉ | C ₂ H ₅ | 95° | 0.027 | 0.10 | -0.76 |
| III ^c | C ₃ H ₇ | C ₄ H ₉ | 103° | 0.0028 | 0.024 | -0.85 |
| IV ^d | C ₄ H ₉ | C ₄ H ₉ | 119° | 0.0073 | 1.5 | -0.99 |
| V ^e | C ₃ H ₇ | CH(CH ₃) ₂ | 74° | 0.11 | 0.80 | -0.91 |
| VI ^f | C ₄ H ₉ | CH ₃ | 83° | 0.039 | 0.30 | -0.69 |
| VII ^g | C ₂ H ₅ | CH(CH ₃) ₂ | 60° | 0.30 | 1.4 | -0.70 |
| VIII ^h | C ₃ H ₇ | CH ₃ | 59° | 0.045 | 0.22 | -0.88 |
| IX ^d | C ₃ H ₇ | C ₃ H ₇ | 92° | 0.049 | 0.23 | -0.99 |
| X ⁱ | C ₄ H ₉ | C ₄ H ₉ | 110° | 0.041 | 0.14 | -0.97 |
| XI ^j | C ₆ H ₁₃ | C ₆ H ₁₃ | 145° | 0.0052 | 0.074 | -0.68 |
| Diethyltoluamide | | | 100° | 0.031 | 0.10 | -0.81 |
| <i>N,N'</i> -Dihexamethylenecarbamide | | | 130° | 0.00081 | 0.056 | -0.83 |

^a Anal.—Calc. for C₇H₁₄N₂O: C, 68.37; H, 12.37; N, 12.32. Found: C, 68.32; H, 12.56; N, 12.24. ^b Anal.—Calc. for C₁₃H₂₆N₂O: C, 68.37; H, 12.36; N, 12.27. Found: C, 68.22; H, 12.55; N, 12.12. ^c Anal.—Calc. for C₁₃H₂₆N₂O: C, 70.25; H, 12.58; N, 10.93. Found: C, 70.36; H, 12.74; N, 10.96. ^d See *Experimental*. ^e Anal.—Calc. for C₁₃H₂₆N₂O: C, 68.37; H, 12.36; N, 12.27. Found: C, 68.17; H, 12.41; N, 12.37. ^f Anal.—Calc. for C₁₁H₂₄N₂O: C, 65.95; H, 12.08; N, 13.99. Found: C, 65.95; H, 12.19; N, 14.00. ^g Anal.—Calc. for C₁₁H₂₄N₂O: C, 65.95; H, 12.08; N, 13.99. Found: C, 65.72; H, 12.33; N, 13.87. ^h Anal.—Calc. for C₉H₂₀N₂O: C, 62.74; H, 11.70; N, 16.27. Found: C, 62.66; H, 11.94; N, 16.08. ⁱ Anal.—Calc. for C₁₁H₂₂N₂O: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.43; H, 11.29; N, 14.07. ^j Anal.—Calc. for C₁₅H₃₀N₂O: C, 70.81; H, 11.89; N, 11.01. Found: C, 70.43; H, 11.73; N, 10.87.

through the stirred solution until approximately 9 g had been collected (0.039 *M*). Potassium carbonate (25.6 g, 0.186 mole) was then added, and the flask was fitted with a nitrogen inlet–outlet, a reflux condenser, and an addition funnel. The stirrer was started, and dibutylamine (15.6 ml, 0.093 mole) was added dropwise over 30 min. Occasional cooling was necessary to ensure that the temperature did not rise above 35°. After the addition was complete, the solution was stirred at room temperature for 3 hr. Another 15.65 ml of dibutylamine was then added, and the solution was refluxed for 3 hr.

The cooled reaction mixture then was filtered to remove potassium carbonate–potassium chloride, evaporated *in vacuo*, and distilled. Redistillation after stripping off benzene after ethanol was added gave a liquid, bp 119°/0.5 mm Hg.

Anal.—Calc. for C₁₇H₃₆N₂O: C, 77.77; H, 12.76; N, 9.85. Found: C, 77.92; H, 12.88; N, 9.84.

Preparation of *N,N'*-Dipropylmethoxycarbonylethylenediamine—Preparation of *N,N'*-dipropyl-1,3-diaza-2-cyclopentanone (IX) was *via* the carbamate *N,N'*-dipropylmethoxycarbonylethylenediamine, which was prepared as follows. A 1-liter, three-necked, round-bottom flask was fitted with a thermometer, an addition funnel, a magnetic stirrer, a reflux condenser, and a heating mantle. The diamine (25 g, 0.174 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 (16.4 g, 0.174 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 at room temperature overnight. The methanol was removed at reduced pressure, and the residue was taken up in methylene chloride (300 ml), filtered to remove the hydrochloride salt of the starting material (4.71 g), and evaporated *in vacuo*.

The residue was dissolved in distilled water, acidified (pH 3), and extracted with ether (three times) to yield Fraction E₁. The aqueous solution was basified with 10% NaOH and reextracted with ether (three times), affording Fraction E₂. Fraction E₁ was dried over sodium sulfate and evaporated *in vacuo*. After distillation, 7.25 g of the dicarbamate was obtained. Fraction E₂, after removal of the solvent *in vacuo*, yielded the monocarbamate intermediate.

Preparation of *N,N'*-Dipropyl-1,3-diaza-2-cyclopentanone (IX)—A 500-ml, three-necked flask was fitted with a Y-tube nitrogen inlet, an ammonia inlet, a dry ice condenser, a gas bubbler, and a magnetic stirrer. The nitrogen was started, and the apparatus flamed out. After cooling under nitrogen, the condenser was charged with dry ice, and ammonia (1) (150 ml) was collected in the flask. Ferric nitrate nonahydrate (50 mg) was added, and the ammonia solution turned light brown. A small piece of sodium (50 mg) was added, and the solution was stirred at -33° until the blue color had disappeared and a black precipitate of catalyst formed.

The remainder of the sodium (0.93 g, 0.04 mole) was then added in portions over 10 min. After the blue color was discharged (0.5 hr), a so-

lution of the carbamate (4.0 g, 0.02 mole) in anhydrous ether (10 ml) was added dropwise from the addition funnel over 30 min. The black solution was then stirred at -33° for 4 hr, and the ammonia was allowed to evaporate overnight under nitrogen.

The residue was dissolved in a water–ether slurry and transferred to a separator. The layers were separated, and the organic phase was washed with ether twice. The combined ether layers were dried (magnesium sulfate), evaporated *in vacuo*, and distilled to afford the desired product, 3.0 g, bp 63–66°/0.08 mm Hg.

Anal.—Calc. for C₉H₁₈N₂O: C, 63.49; H, 10.65; N, 16.46. Found: C, 61.97; H, 10.68; N, 16.04.

RESULTS AND DISCUSSION

Table I gives the structures, boiling points, and repellency data for the compounds. Those repellents for *A. aegypti* (yellow fever mosquito) having ED₅₀ and ED₉₀ values lower than the standard repellent (diethyltoluamide) are candidates for further evaluation in other tests for repellency. However, prior to application to human skin, preliminary toxicology studies must be performed.

Compared to diethyltoluamide, II–IV, VI, and XI had lower or comparable ED₅₀ values and II, III, and XI had lower or comparable ED₉₀ values. Compared to *N,N'*-hexamethylenecarbamide, III and XI had as good or better ED₉₀ values.

The relationship between boiling point and repellency in this test is not as clear as in prior studies (3), but maximum effectiveness in terms of ED₅₀ or ED₉₀ values appeared to peak with the *N*-substituted ureas around 100° at 0.5 mm Hg, which is very similar to the value found with analogs of diethyltoluamide by skin testing (3). With the cyclic urea derivatives, the peak activity was found around 145° at 0.5 mm Hg, closer to that of *N,N'*-dihexamethylenecarbamide.

Further study of the most active of these compounds may yield improved topical repellents for mosquitoes and point the way to improved compounds in this series by variation of their volatility.

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