ARTICLES

ALICYCLIC CARBOXAMIDES FROM HETEROCYCLIC AMINES AS REPELLENTS FOR *AEDES AEGYPTI* AND *ANOPHELES QUADRIMACULATUS*

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ABSTRACT. Of 45 amides synthesized from five alicyclic carboxylic acids and nine heterocyclic amines, 39 were Class 5 repellents (effectiveness >21 days) against *Aedes aegypti* (L.) or *Anopheles quadrimaculatus* Say when tested on cloth and are considered promising mosquito repellents. Eighteen of the amides were highly effective, providing 70 or more days of protection against one or both mosquito species. The cyclohexane-carboxamides of 2-, 3-, and 4-methylpiperidine, 2-ethylpiperidine, and 2,6-dimethylpiperidine were the most effective repellents against *Ae. aegypti*, providing 104 days of protection. 4 - (Bicyclo[2.2.1]hept - 5 - en - 2 - ylcarbonyl) - 2,6 - dimethylmorpholine was exceptionally effective against *An. quadrimaculatus*, providing 190 days of protection.

INTRODUCTION

Over the past few years we have prepared a number of amides of heterocyclic amines that are promising mosquito repellents (McGovern et al. 1974, 1975). Most recently we described a number of amides of alicyclic carboxylic acids that are effective as repellents for *Aedes aegypti* (L.) and *Anopheles quadrimaculatus* Say (McGovern et al. 1978). The majority of the promising repellents were derivatives of the heterocyclic amines, pyrrolidine, piperidine, and hexahydro-1*H*-azepine. Many of these chemicals were also effective repellents for the stable fly, *Stomoxys calcitrans* (L.), and various blackfly species, *Simuliidae* spp. (Schreck et al. 1978, 1979). Because of their effectiveness as repellents for mosquitoes and other biting flies, we have continued to synthesize and evaluate other chemicals of this type. This paper reports repellency data for 45 amides synthesized from 5 alicyclic acids and 9 heterocyclic amines.

MATERIALS AND METHODS

The chemicals were synthesized by the standard reaction between an alicyclic acid chloride and an appropriate amine and purified by conventional procedures, as described by Schreck et al. (1977). The purity of the chemicals was >95% by gas-liquid chromatographic analysis.

Chemicals were tested by placing a treated cotton stocking (test materials were applied to 0.03 m^2 of stocking at a rate of 3.3 g/0.1 m^2) over an untreated nylon stocking on the arm of a human subject and exposing the arm for a 1-min peroid in a cage of ca. 1500 5-to-8-day-old *Ae. aegypti* or *An. quadrimaculatus* mosquitoes (McGovern et al. 1975, 1978). Test exposures were repeated at 24 hr and then at weekly intervals until 5 bites were received in 1 min. Days to the 1st bite and to 5 bites in 1 min were recorded. A standard repellent, dimethyl phthalate, was tested concurrently and was effective for 11–21 days (Class 4) against both mosquito species. Effectiveness of the materials is rated as follows: Class 1. 0-day protection; Class 2. effective for 1–5 days; Class 3. Effective for 6–10 days; Class 4. effective for 11–21 days; Class 5. effective for more than 21 days.

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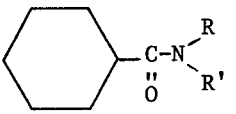
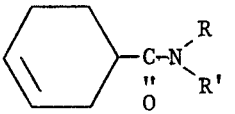
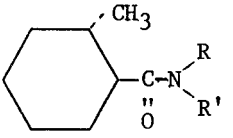
RESULTS AND DISCUSSION

Table 1 lists repellency data for 5 series of alicyclic carboxamides from 9 heterocyclic amines including 5 alkyl-substituted piperidines, 1 unsaturated piperidine, 1 piperazine, and 2 morpholines. Previously published data for the 5 parent piperidine derivatives (1st chemical of each series) are included for comparison. The good to excellent repellency found with the pyrrolidine, piperidine, and hexahydro-1*H*-azepine derivatives by Mc Govern et al. (1978) is also found with the carboxamide derivatives of the heterocyclic amines used in this study. In each series, one or more of the chemicals equalled or exceeded the repellency of the parent piperidine derivative, and 39 of the 45 amides were Class 5 repellents against 1 or both mosquito species. The best repellents against

Table 1. Repellency of alicyclic carboxamides of heterocyclic amines against *Aedes aegypti* and *Anopheles quadrimaculatus*.

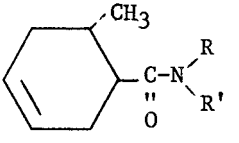
No.	*Ae. aegypti* Class	*Ae. aegypti* Days to 1st bite	*Ae. aegypti* Days to 5 bites	*An. quadrimaculatus* Class	*An. quadrimaculatus* Days to 1st bite	*An. quadrimaculatus* Days to 5 bites
Series A. 						
1. 1-Piperidyl*	5	30	38	5	30	30
2. 2-Methyl-1-piperidyl	5	104	104	5	111	111
3. 3-Methyl-1-piperidyl	5	104	104	5	22	22
4. 4-Methyl-1-piperidyl	5	52	104	5	0	22
5. 2-Ethyl-1-piperidyl	5	104	104	5	1	22
6. 2,6-Dimethyl-1-piperidyl	5	104	104	5	1	37
7. 1,2,3,6-Tetrahydro-1-pyridinyl	4	15	15	4	15	15
8. 4-Methyl-1-piperazinyl	4	7	15	5	7	111
9. 4-Morpholinyl	2	0	1	5	27	27
10. 2,6-Dimethyl-4-morpholinyl	5	15	28	5	35	35
Series B. 						
11. 1-Piperidyl*	5	21	28	5	28	48
12. 2-Methyl-1-piperidyl	5	69	69	5	83	83
13. 3-Methyl-1-piperidyl	5	36	36	5	36	51
14. 4-Methyl-1-piperidyl	4	20	20	5	83	83
15. 2-Ethyl-1-piperidyl	5	83	83	5	83	83
16. 2,6-Dimethyl-1-piperidyl	5	36	36	5	36	36
17. 1,2,3,6-Tetrahydro-1-pyridinyl	5	36	36	5	63	63
18. 4-Methyl-1-piperazinyl	5	28	28	5	63	83
19. 4-Morpholinyl	1	0	0	5	35	35
20. 2,6-Dimethyl-4-morpholinyl	3	8	8	5	22	22

Series C.



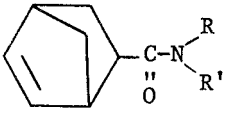
21. 1-Piperidyl*	5	21	28	4	13	13
22. 2-Methyl-1-piperidyl	5	23	43	1	0	0
23. 3-Methyl-1-piperidyl	5	23	51	1	0	0
24. 4-Methyl-1-piperidyl	5	36	36	4	21	21
25. 2-Ethyl-1-piperidyl	5	51	71	1	0	0
26. 2,6-Dimethyl-1-piperidyl	5	1	23	1	0	0
27. 1,2,3,6-Tetrahydro-1-pyridinyl	4	8	15	3	8	8
28. 4-Methyl-1-piperazinyl	2	1	1	5	36	50
29. 4-Morpholinyl	5	36	77	5	64	71
30. 2,6-Dimethyl-4-morpholinyl	5	28	28	4	15	15

Series D.



31. 1-Piperidyl*	5	33	41	2	1	1
32. 2-Methyl-1-piperidyl	5	23	51	5	0	23
33. 3-Methyl-1-piperidyl	5	36	36	4	0	21
34. 4-Methyl-1-piperidyl	5	36	36	5	8	36
35. 2-Ethyl-1-piperidyl	3	1	8	3	8	8
36. 2,6-Dimethyl-1-piperidyl	3	1	8	3	8	8
37. 1,2,3,6-Tetrahydro-1-pyridinyl	4	15	15	2	0	1
38. 4-Methyl-1-piperazinyl	1	0	0	3	0	8
39. 4-Morpholinyl	5	8	22	5	36	105
40. 2,6-Dimethyl-4-morpholinyl	5	1	28	5	22	22

Series E.



41. 1-Piperidyl*	5	70	70	5	70	91
42. 2-Methyl-1-piperidyl	5	70	70	5	0	76
43. 3-Methyl-1-piperidyl	5	35	70	5	0	49
44. 4-Methyl-1-piperidyl	5	70	70	5	0	77
45. 2-Ethyl-1-piperidyl	5	21	34	5	47	47
46. 2,6-Dimethyl-1-piperidyl	5	1	28	4	20	20
47. 1,2,3,6-Tetrahydro-1-pyridinyl	5	28	28	4	20	20
48. 4-Methyl-1-piperazinyl	5	28	28	5	47	47
49. 4-Morpholinyl	1	0	0	5	47	47
50. 2,6-Dimethyl-4-morpholinyl	5	0	34	5	20	190

* Data from McGovern et al. (1978) are included for comparison.

Ae. aegypti, with 1 exception, are found among the alkyl-substituted piperidine amides of each series. 1-(Cyclohexanecarbonyl)-2-methylpiperidine (no. 2), -3-methylpiperidine (no. 3), -2-ethylpiperidine (no. 5), and -2,6-dimethylpiperidine (no. 6) were the most effective, providing 104 days of protection before both the 1st and 5th bite. The 4-methylpiperidine derivative (no. 4) also provided 104 days of protection before the 5th bite. Other amides that provided protection worthy of note are no. 12 and 15 (Series B), no. 25 and 29 (Series C), and no. 42, 43, and 44 (Series E). In all, 32 chemicals were Class 5 repellents for *Ae. aegypti.*

Four chemicals provided over 100 days of protection against *An. quadrimaculatus.* 4 - (Bicyclo[2.2.1]hept - 5 - en - 2 - ylcarbonyl) - 2,6 - dimethylmorpholine (no. 50) was outstanding, providing 190 days of protection. 1 - (Cyclohexanecarbonyl) - 2 - methylpiperidine, 1 - (cyclohexanecarbonyl) - 4 - methylpiperazine, and 4 - (6 - methyl - 3 - cyclohexen - 1 - ylcarbonyl) morpholine (no. 2, 8, and 39) provided 111, 111, and 105 days of protection, respectively. Amide no. 2 also provided 111 days of protection before the first bite. Other amides that provided protection worthy of note are no. 12, 14, 15, and 18 (Series B), no. 29 (Series C), and no. 42 and 44 (Series E).

In general, the repellency behavior of the 6 piperidine derivatives within each series parallels that reported earlier for other heterocyclic amides (McGovern et al. 1978). When series are compared, the data of the piperidine derivatives of Series A, B, C, and D reveal that unsaturation reduces repellency against *Ae. aegypti* and increases it against *An. quadrimaculatus,* with a few exceptions. Addition of a methyl group in a *trans* configuration, adjacent to the amide function, caused a reduction in activity, particularly against *An. quadrimaculatus* (Series C and D compared to A and B). Maximum steric interference occurs between the two groups in this configuration. If the amide group is assumed to be a major contributor to repellent action, the steric interference might be responsible for the observed decrease in activity by reducing interaction of the amide function with a sensory receptor site. Locking an adjacent "methyl" group into a bridged methylene structure, as in the acid moiety of the chemicals of Series E, prevents steric interference with the amide function. The result is a substantial increase in the activity of the piperidine amides of this series when compared with those in Series C or D. It should be pointed out, however, that even minor structural modifications in the alicyclic portion of the molecule, such as unsaturation or a ring bridging, considerably change the shape of that ring, whereas substitution of other groups in place of hydrogen increases steric interactions but does not affect the basic ring shape.

The last 3 amides of each series differ from the others in having a 2nd heteroatom in the amine moiety; *An. quadrimaculatus* was generally more strongly repelled by these derivatives than was *Ae. aegypti.* Three of the four amides that provided over 100 days of protection against *An. quadrimaculatus* are from this group; 13 of the 15 chemicals are Class 5 repellents, while 8 of 15 are Class 5 against *Ae. aegypti.* The variation in the effect of this group of chemicals against *An. quadrimaculatus* was particularly noticeable in Series C where the piperidine derivatives were ineffective. The change in repellency of the 4-methylpiperazine and 2,6-dimethylmorpholine derivatives as the structure changes from series to series parallels, in most cases, that of the piperidines. Surprisingly, the repellency of the morpholine derivatives changes in exactly the opposite manner. Addition of a methyl group in the alicyclic acid moiety (no. 29 and 39, Series C and D) greatly enhances the repellency over that of the compounds in Series A and B (no. 9 and 19). The spatial configuration of the piperidine, piperazine, and morpholine groups is essentially the same so the gross molecular structure or shape of the

molecule is probably not responsible for these variations in repellency. A major difference between these heterocyclic groups is the presence of a 2nd heteroatom with unshared electron pairs in the morpholine and piperazine moiety that is missing in the piperidine moiety. The oxygen atom of the morpholine molecule has 2 pairs of unshared electrons, whereas the nitrogen atom of the piperazine ring has 1. We do not know that such electron pairs play a part in any chemical-sensory receptor site interaction. However, the oxygen atom of the 2,6-dimethylmorpholine moiety has 2 adjacent methyl groups and the corresponding nitrogen of the 4-methylpiperazine group is methylated. These steric factors may adversely affect interaction of these heteroatoms with potential receptor sites in contrast to the unencumbered oxygen of the unsubstituted morpholine moiety. Another consideration is that the presence of substitution at the 2nd heteroatom and the extent of this substitution will affect electron distribution in the molecule; changes in biological activity would be expected to occur because the nearby amide linkage, which appears to be essential for activity, would be affected.

References Cited

McGovern, T. P., H. K. Gouck, G. S. Burden, R. Sarmiento, M. Beroza and C. H. Schmidt. 1974. *N,N*-Substituted n-alkanesulfonamides as repellents for the yellow fever mosquito and the German cockroach. J. Econ. Entomol. 67:71–73.

McGovern, T. P., C. E. Schreck, J. Jackson and M. Beroza. 1975. *n*-Acylamides and *n*-alkylsulfonamides from heterocyclic amines as repellents for yellow fever mosquitoes. Mosquito News 35(2):204–210.

McGovern, T. P., C. E. Schreck and J. Jackson. 1978. Mosquito repellents: Alicyclic acid amides as repellents for *Aedes aegypti* (L.) and *Anopheles quadrimaculatus* Say. Mosquito News 38(3):346–349.

Schreck, C. E., T. P. McGovern and N. Smith. 1978. Repellency of selected esters and amides of four alicyclic acids against the stable fly *Stomoxys calcitrans* (Diptera: Muscidae). J. Med. Entomol. 14(5):589–91.

Schreck, C. E., N. Smith, T. P. McGovern, D. Smith and K. Posey. 1979. Repellency of selected compounds against black flies. J. Med. Entomol., in press.

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