n-ACYLAMIDES AND *n*-ALKYLSULFONAMIDES FROM HETEROCYCLIC AMINES AS REPELLENTS FOR YELLOW FEVER MOSQUITOES [1]

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ABSTRACT. Of 91 *n*-acylamides and *n*-alkylsulfonamides from heterocyclic amines that were synthesized and tested, 13 were highly effective repellents for the yellow fever mosquito *Aedes aegypti* (L.) providing over 100 days of protection on cloth. The 3 most effective repellents and the days of protection each provided (in parentheses) were 4-nonanoylmorpholine (318), 4-octanoylmorpholine (219), and 2,6-dimethyl-4-nonanoylmorpholine (190).

INTRODUCTION

USDA scientists have been interested in evaluating repellents against biting flies, particularly mosquitoes, for many years. Although effective repellents have been found, those that have been approved for application to the skin have certain disadvantages such as not being effective for long enough periods of time and being subject to loss by abrasion, evaporation, absorption, and immersion in water. Moreover, all cause a stinging sensation when they contact the eyelids and lips, and are effective only when they are present on the skin or clothing in relatively large quantities (Weidhaas 1972). Efforts to find and develop broad-spectrum personal-use repellents that would be more satisfactory than those now available have therefore continued. Furthermore, recent efforts to minimize the use of conventional insecticides have increased the need for alternate methods of insect control, and the use of behavior-modifying chemicals, such as insect repellents, for personal protection has assumed greater importance.

In previous studies (Alexander and Beroza 1963), aliphatic amides derived from pyrrolidine, piperidine, and hexahydro-1*H*-azepine were shown to be effective repellents against the yellow fever mosquito, *Aedes aegypti* (L.) as were aliphatic sulfonamides from the same heterocyclic amines (McGovern et al. 1974). We now report the data concerning the repellency of 67 *n*-acyl derivatives and 24 *n*-alkylsulfonyl derivatives of heterocyclic amines that were prepared and evaluated against mosquitoes.

MATERIALS AND METHODS

CHEMICALS. The amides were synthesized and purified by conventional procedures. The purity of the chemicals was verified as $> 95\%$ by gas chromatography and infrared spectral analysis.

MOSQUITO REPELLENCY TESTS. Test materials were applied to a measured portion of a woman's cotton stocking as 1% solutions of the candidate compound in a volatile solvent, usually acetone, at the rate of 3.3 g of the compound per 0.1 m^2 of cloth. Two hours after treatment, the stocking was placed on the arm of a human subject and exposed for 1 min in a cage of ca. 1,500 *A. aegypti* mosquitoes. If fewer than 5 mosquitoes bit the subject through the stocking, the test was repeated at 24 hr and then at weekly intervals until 5 bites were received in 1 min. A standard repellent, dimethyl phthalate, was tested concurrently with these materials and was effective for 11 to 22 days. An exceptionally effective repellent, 2-butyl-2-ethyl-1,3-propanediol, which is used in the U. S. military clothing repellent mixture, was generally effective for 196

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days. Effectiveness of the chemicals was 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.

RINSE AND WASH TESTS. Mosquito repellents that provided 11 or more days protection on cloth were subjected to rinsing tests. A freshly treated stocking was rinsed for 15 min in cool water. The stocking was then dried and placed on the arm of a human subject and exposed for 1 min in a cage of *A. aegypti*. If less than 5 bites were received, the rinse test was repeated. If the treatment was still effective after the second rinse, the stocking was subjected to wash tests. In these tests, the stocking was washed for 15 min in hot, soapy water at 50° C, rinsed for 5 min, dried, and tested again. The wash tests were repeated until the treatment became ineffective.

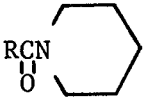
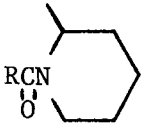
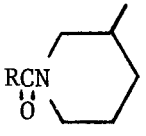
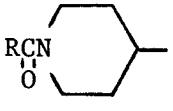
Of the thousands of compounds that have been evaluated as repellents against mosquitoes by the Gainesville laboratory, relatively few have withstood the rinse and wash tests.

RESULTS AND DISCUSSION

Table 1 lists repellency data for 70 *n*-acyl derivatives of 10 heterocyclic amines comprising 7 piperidines, 1 piperazine, and 2 morpholines. The previously published data for 3 amides are included in series A for comparison. In each series, as the molecular weight of the amide increased from butyl through decyl, the activity increased, peaked, and declined. With one exception, the highest activity in series A through I was found with the homolog that had a total of 14 carbon atoms in its molecule (or the approximate equivalent in series H and I). The exception occurred in series G, (activity was low relative to the other series) in which the highest activity was found in the C_{12}, C_{13}, and C_{14} homologs. Overall, 12 amides showed excellent repellency and gave more than 100 days of protection, and 3 of these were outstanding. The most effective repellent was 4-nonanoylmorpholine (no. 62), which gave 318 days of protection; indeed, the chemical gave 143 days of protection before the first bite. The next 2 most effective compounds were 4-octanoylmorpholine (no. 61) and 2,6-dimethyl-4-nonanoylmorpholine (no. 69); they were effective for 219 and 190 days, respectively. A fourth material, 4-heptanoyl-2,6-dimethylmorpholine (no. 67), persisted for 120 days before the first bite was recorded and was effective for 141 days.

Some observations can be made concerning the effect on repellency of structural changes made relative to the parent piperidine series (A). In all but 1 series, the highest activity was found when the molecular weight of the amide was at or near 225 (e.g., those cited with 14 carbon atoms); however, maximum effectiveness and the number of effective compounds in each series varied. Addition of a methyl group to the hetero ring (Series B, C, and D) resulted in a moderate to substantial increase in effectiveness; the position of the methyl group also affected activity. Thus the 2- and 3-methyl substituted amides, which were about equal in maximum effectiveness, were more effective than the 4-methyl substituted amides. However, the addition of an ethyl group or 2 methyl groups to the ring (Series E and F) resulted in a moderate to substantial decrease in repellency. Series F had only 2 Class 5 repellents; the other members of this series were ineffective. Also, a noticeable difference in effectiveness was observed between series E and B: replacing a methyl group with an ethyl group caused a 39% reduction in the maximum effectiveness. Although series G contained 5 Class 4 or 5 repellents, they were of relatively low persistence compared with other compounds tested. Thus, the introduction of a center of unsaturation into the piperidine ring (cf. Series A) caused a 67% reduction in maximum effectiveness. In series H, 1 of the ring carbon atoms was replaced with

Table 1. Repellency of acyl derivatives of heterocyclic amines against yellow fever mosquitoes.

Chem. no.	Series RC–(=O)	Class	Days to 1st bite	Days to 5th bite	Minutes of rinsing survived
	A. 				
1.	Butyryl	2	1	1	..
2.	Pentanoyl	3	1	8	..
3.	Hexanoyl[a]	4	15	15	0
4.	Heptanoyl	5	37	37	0
5.	Octanoyl[a]	5	50	50	15
6.	Nonanoyl[a]	5	92	106	0
7.	Decanoyl	5	23	37	30[b]
	B. 				
8.	Butyryl	3	8	8	..
9.	Pentanoyl	3	8	8	..
10.	Hexanoyl	4	15	15	0
11.	Heptanoyl	5	57	57	0
12.	Octanoyl	5	23	140	30
13.	Nonanoyl	5	0	36	15
14.	Decanoyl	1	0	0	..
	C. 				
15.	Butyryl	2	1	1	..
16.	Pentanoyl	3	8	8	..
17.	Hexanoyl	4	15	15	0
18.	Heptanoyl	5	50	57	15
19.	Octanoyl	5	1	147	30
20.	Nonanoyl	1	0	0	..
21.	Decanoyl	1	0	0	..
	D. 				
22.	Butyryl	2	1	1	..
23.	Pentanoyl	2	1	1	..
24.	Hexanoyl	5	22	22	0
25.	Heptanoyl	5	58	65	15
26.	Octanoyl	5	31	121	30
27.	Nonanoyl	4	1	15	15
28.	Decanoyl	2	1	1	..

[a] Data from Alexander and Beroza (1963) are included for comparison.
[b] Also withstood a 15 min. hot, soapy water wash.

Table 1 (Continued)

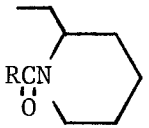
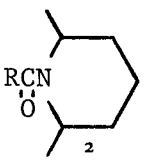
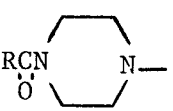
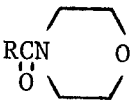
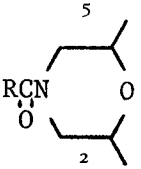
Chem. no.	Series RC(=O)–	Class	Days to 1st bite	Days to 5th bite	Minutes of rinsing survived
	E. 				
29.	Butyryl	2	1	1	..
30.	Pentanoyl	5	22	22	0
31.	Hexanoyl	5	36	36	0
32.	Heptanoyl	5	51	86	15
33.	Octanoyl	4	1	15	15
34.	Nonanoyl	2	1	1	..
35.	Decanoyl	1	0	0	..
	F. 				
36.	Butyryl	2	1	1	..
37.	Pentanoyl	2	1	1	..
38.	Hexanoyl	5	30	30	0
39.	Heptanoyl	5	0	58	30
40.	Octanoyl	1	0	0	..
41.	Nonanoyl	1	0	0	..
42.	Decanoyl	2	1	1	..
	G. 				
43.	Butyryl	1	0	0	..
44.	Pentanoyl	4	15	15	0
45.	Hexanoyl	5	15	32	0
46.	Heptanoyl	5	35	35	0
47.	Octanoyl	5	15	35	15
48.	Nonanoyl	5	22	35	30
49.	Decanoyl	3	1	8	..
	H. 				
50.	Butyryl	2	1	1	..
51.	Pentanoyl	4	8	13	0
52.	Hexanoyl	5	27	27	0
53.	Heptanoyl	5	15	65	0
54.	Octanoyl	5	1	155	0
55.	Nonanoyl	5	1	44	0
56.	Decanoyl	2	1	1	..

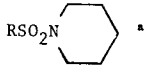
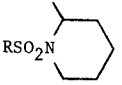
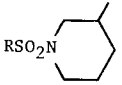
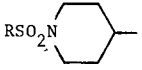
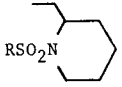
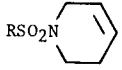
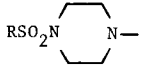
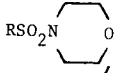
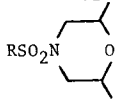
Table 1 (Continued)

Chem. no.	Series RC(=O)–	Class	Days to 1st bite	Days to 5th bite	Minutes of rinsing survived
	I. 				
57.	Butyryl	2	1	1	..
58.	Pentanoyl	5	8	22	0
59.	Hexanoyl	5	22	29	0
60.	Heptanoyl	5	64	78	0
61.	Octanoyl	5	37	219	0
62.	Nonanoyl	5	143	318	0
63.	Decanoyl	5	71	143	0
	J. 				
64.	Butyryl	2	1	1	..
65.	Pentanoyl	4	17	17	0
66.	Hexanoyl	5	44	44	0
67.	Heptanoyl	5	120	141	0
68.	Octanoyl	5	0	141	0
69.	Nonanoyl	5	10	190	30
70.	Decanoyl	5	30	113	30

a methyl-substituted nitrogen atom, which made it comparable with series D as well as A. This structural change produced the third most active series of the present study having 5 Class 4 or 5 repellents, 1 of which (no. 54) was the fourth most active repellent listed in Table 1. When 1 of the ring carbon atoms was replaced by an oxygen atom (Series I and J), both the maximum and overall effectiveness within the series were dramatically increased. Thus 6 of the 7 homologs in series I were Class 5 repellents and 6 of the 7 in J were Class 4 or 5 repellents; and these were the only series with more than 1 compound that gave over 100 days of protection. Series I included 2 of the 3 homologs that possessed outstanding persistence, no. 61 and no. 62. Thus, 7 compounds in these 2 series provided protection from 113 to 318 days.

Table 2 presents the data on repellency for the ethyl-, propyl-, and butylsulfonamides from 9 heterocyclic amines. Data for series K (published previously) are included for comparison. Three of the sulfonamides showed excellent repellency. The most effective was 1-(butylsulfonyl)-3-pipecoline (Series M), which provided 125 days of protection, but 1-(propylsulfonyl)- and 1-(butylsulfonyl)-4-pipecoline (Series N) provided 83 and 90 days of protection, respectively. However, as a class, the sulfonamides were much less effective repellents than the carboxamides of Table 1. The butylsulfonyl derivatives in the pipecoline series (L, M, and N), which have 10 carbon atoms, were the most effective and had a molecular weight of 219, which approximates the molecular weight (225) of the most effective repellents listed in Table 1. Also, the most

Table 2. Repellency of alklsulfonyl derivatives of heterocyclic amines against yellow fever mosquitoes

		R										
		Ethyl				Propyl				Butyl		
			Days to		Minutes		Days to		Minutes		Days to		Minutes
Series	Amide	Class	1st bite	5th bite	of rinsing survived	Class	1st bite	5th bite	of rinsing survived	Class	1st bite	5th bite	of rinsing survived
K.		2	1	1	..	2	1	1	..	5	50	70	0
L.		3	8	8	..	5	25	25	0	5	62	69	15
M.		5	28	28	0	5	57	57	0	5	42	125	30
N.		5	21	21	0	5	21	83	15	5	42	90	30
O		4	20	20	0	5	57	57	0	5	8	42	0
P.		4	1	15	0	5	15	29	0	5	8	29	0
Q.		1	0	0	..	2	0	1	..	2	0	1	..
R.		1	0	0	..	1	0	0	..	1	0	0	..
S.		1	0	0	..	1	0	0	..	1	0	0	..

effective 2-ethylpiperidine (Series O) was the propylsulfonyl derivative, also a C_{10} compound, and similarly as found with the carboxamides of Table 1 there is a decrease in effectiveness from that of the pipecoline series. Comparison of the repellency data of the butylsulfonamides of series K and O showed a decrease in effectiveness similar to that observed for analogous compounds listed in Table 1, though the ethyl and propyl homologs of series O showed increased activity. However it was in series Q, R, and S that the marked differences between the carboxamides and sulfonamides occurred. In these 3 series, all 3 derivatives were completely inactive; in the acyl series reported in Table 1, the piperazine and morpholine derivatives were generally outstanding repellents. We have no explanation for this reversal, particularly since the substitution of a sulfonyl group for a carbonyl in the piperidine series (K through P) had no marked adverse effect.

Although some of these repellents were highly effective in the present test, they cannot be recommended for general use until further testing and toxicological studies have established their safety.

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