MOSQUITO REPELLENTS: ALICYCLIC AMIDES AS REPELLENTS FOR *AEDES AEGYPTI* AND *ANOPHELES QUADRIMACULATUS*

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ABSTRACT. Of 30 amides synthesized from 5 alicyclic carboxylic acids, 6 were highly effective repellents for *Aedes aegypti* (L.) or *Anopheles quadrimaculatus* Say when tested on cloth. 1-1(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl) hexahydro - 1*H* - azepine was the most effective repellent; it provided 128 and 111 days of protection against *Ae. aegypti* and *An. quadrimaculatus*, respectively.

INTRODUCTION

In a continuing effort to find and develop improved insect repellents for personal use, USDA scientists have synthesized and evaluated large numbers of candidate materials. This effort has intensified over the past few years because of the increased importance of alternate measures for insect control. We previously reported that a number of aliphatic amides and sulfonamides derived from heterocyclic amines were highly effective repellents for the yellow fever mosquito, *Aedes aegypti* (L.), when applied to cloth (McGovern et al. 1974, 1975). We now report data for 30 alicyclic carboxamides tested as repellents against *Ae. aegypti* and *Anopheles quadrimaculatus* Say.

MATERIALS AND METHODS

CHEMICALS. The amides were synthesized by using the standard reaction between an alicyclic acid chloride and an appropriate amine and were purified by conventional procedures. The purity of the chemicals was > 95% by gas chromatographic analysis.

MOSQUITO REPELLENCY TESTS. Tests

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were performed as previously described (McGovern et al. 1975). Test materials were applied at the rate of 3.3 g of compound per 0.1 m^2 cloth to a measured portion (0.03 m^2) of a cotton stocking as 10% solutions in acetone or other volatile solvent. After 2 hr, the treated stocking was placed over an untreated nylon stocking on the arm of a human subject and exposed for 1 min in a cage containing ca. 1,500 5 to 8-day old *Ae. aegypti* or *An. quadrimaculatus*. The test exposure was repeated at 24 hr and then at weekly intervals until 5 bites were received in 1 min. Days to the first bite and to 5 bites were recorded. 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. Between tests, the treated stockings were placed on a rack at room temperature, and evaporation was allowed to continue. A standard repellent, dimethyl phthalate, was tested concurrently and was effective for 11 to 21 days (Class 4) against both mosquito species.

RINSE AND WASH TESTS. Candidate repellents that provided 11 or more days of protection were subjected to rinsing tests in which freshly treated stockings were rinsed for 15 min in cool water, dried, and tested against the mosquitoes as before. If fewer than 5 bites were received in 1 min, the rinse test was repeated. Compounds surviving 2 rinses were washed for 15 min in hot, soapy water, rinsed for 5 min, dried, and tested again.

RESULTS AND DISCUSSION

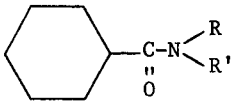
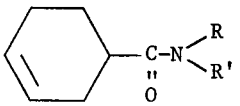
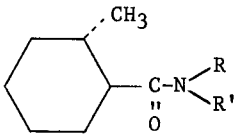
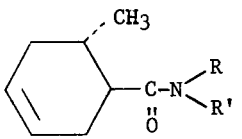
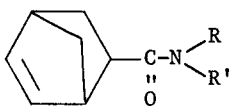
Repellency data for 5 series of alicyclic carboxamides that includes derivatives of the dialkyl amines, diethyl-, dipropyl-, and dibutyl-, and of the heterocyclic amines, pyrrolidine, piperidine, and hexahydro -1*H* - azepine are reported in Table 1. The present study includes *An. quadrimaculatus* mosquitoes in addition to *Ae. aegypti*, the sole test insect in our previous reports. In general, the amides from the heterocyclic amines provided good to exceptionally effective protection against both species. All 15 amides derived from the cyclic amines were Class 5 repellents against *Ae. aegypti*, and the hexahydro - 1*H* - azepine derivatives in Series A, B, and E, 1 - (cyclohexylcarbonyl)hexahydro - 1*H* - azepine (no. 6), 1 - (3 - cyclohexen - 1 - ylcarbonyl) hexahydro - 1*H* - azepine (no. 12), 1 - (bicyclo [2 . 2 . 1] hept - 5 - en - 2 - ylcarbonyl) hexahydro - 1*H* - azepine (no. 30), and the piperidine derivative of Series E, 1 - (bicyclo [2 . 2 . 1] hept - 5 - en - 2 - ylcarbonyl) piperidine (no. 29), were particularly effective in providing protection against both the 1st and 5th bite. Ten of the cyclic amine derivatives were also Class 5 repellents against *An. quadrimaculatus*. Again, amides no. 12, 29, and 30 were especially effective as were 2 pyrrolidine derivatives, 1 - (cyclohexylcarbonyl) pyrrolidine (no. 4) and 1 - (3 - cyclohexen - 1 - ylcarbonyl) pyrrolidine (no. 10).

Series E was the most effective of the 5 series tested, both in terms of overall persistence and in the number of Class 5 repellents. Four amides in this series are Class 5 repellents against both mosquito species, and 1 - (bicyclo [2 . 2 . 1] hept - 5 - en - 2 - ylcarbonyl) hexahydro - 1*H* - azepine (no. 30), the most effective repellent tested in this study, showed excellent repellency; it provided 128 days of protection against *Ae. aegypti* and 111 days of protection against *An. quadrimaculatus*.

Most of the *N,N*-dialkyl amides were poor repellents. The *N.N* dipropyl amide was generally the most effective of the dialkyl amides and, in Series E (no. 26), was a Class 5 repellent against both species.

Minor structural changes on the alicyclic acid moiety significantly alter the shape of the molecule and thus may alter the way it interacts with a sensory site. In some instances, little alteration in repellent activity accompanies these changes; in others, substantial variations occur. These effects were most marked in the repellency data of the heterocyclic deriva-

Table 1. Repellency of alicyclic carboxamides to *Aedes aegypti* and *Anopheles quadrimaculatus*.

No.	Series R	Series R′	*A. aegypti* Class	*A. aegypti* Days to 1st bite	*A. aegypti* Days to 5 bites		*A. quadrimaculatus* Class	*A. quadrimaculatus* Days to 1st bite	*A. quadrimaculatus* Days to 5 bites
	A.								
1.	C_2H_5	C_2H_5	2	4	4		2	1	1
2.	C_3H_7	C_3H_7	4	15	15		3	8	8
3.	C_4H_9	C_4H_9	3	0	8		1	0	0
4.	—$(CH_2)_4$—		5	30	38		5	38	79
5.	—$(CH_2)_5$—		5	30	38		5	30	30
6.	—$(CH_2)_6$—		5	106	113		5	22	38
	B.								
7.	C_2H_5	C_2H_5	2	1	1		2	1	1
8.	C_3H_7	C_3H_7	4	15	15		4	15	15
9.	C_4H_9	C_4H_9	5	0	30		2	0	1
10.	—$(CH_2)_4$—		5	28	28		5	70	94
11.	—$(CH_2)_5$—		5	21	28		5	28	48
12.	—$(CH_2)_6$—		5	64	87		5	70	70
	C.								
13.	C_2H_5	C_2H_5	3	8	8		2	1	1
14.	C_3H_7	C_3H_7	4	15	15		2	1	1
15.	C_4H_9	C_4H_9	1	0	0		1	0	0
16.	—$(CH_2)_4$—		5	21	28		5	28	28
17.	—$(CH_2)_5$—		5	21	28		4	13	13
18.	—$(CH_2)_6$—		5	28	28		3	6	6
	D.								
19.	C_2H_5	C_2H_5	3	7	7		1	0	0
20.	C_3H_7	C_3H_7	5	27	27		2	1	1
21.	C_4H_9	C_4H_9	1	0	0		1	0	0
22.	—$(CH_2)_4$—		5	27	27		2	1	1
23.	—$(CH_2)_5$—		5	33	41		2	1	1
24.	—$(CH_2)_6$—		5	27	47		2	1	1
	E.								
25.	C_2H_5	C_2H_5	2	1	1		3	8	8
26.	C_3H_7	C_3H_7	5	1	35		5	49	49
27.	C_4H_9	C_4H_9	2	0	1		1	0	0
28.	—$(CH_2)_4$—		5	34	55		5	28	28
29.	—$(CH_2)_5$—		5	70	70		5	70	91
30.	—$(CH_2)_6$—		5	70	128		5	0	111

tives of each series and will be discussed further. There should be little difference in volatility among like members in each series, so much of the change in activity should result from structural changes on the cyclohexane ring.

The introduction of a center of unsaturation into the acid moiety (cf Series A-B and C-D) affects each species differently. Series B was less active than A, series D was more active than C against *Ae. aegypti*, and the hexahydro - 1*H* - azepine derivative was the most active member of each series. Against *An. quadrimaculatus*, Series B was more active than A, series D was less active than C, and the pyrrolidine derivative was the most active member of each series except in Series D, where all of the heterocyclic carboxamides were inactive. Introduction of a methyl group (cf Series A-C and B-D) caused a general decrease in activity against both species of mosquito and was particularly detrimental to the repellent activity against *An. quadrimaculatus*. The chemicals of Series D were essentially nonrepellent to this species. The methyl and carboxamide groups of Series C and D are predominantly in the *trans* configuration in which the diequatorial conformation is favored. If the amide function is a major requirement for repellent activity, close proximity of the more bulky methyl group (vs that of a hydrogen atom) may interfere with its interaction with a sensory receptor site, thus reducing or negating its activity. *An. quadrimaculatus* may be more sensitive to this interference than *Ae. aegypti*. The amides of Series E have the same molecular weights as their counterparts in Series D. However, because the bicyclo structure is quite different from that of the cyclohexene group, a meaningful comparison of the data of the 2 series cannot be made. In the bicyclic compounds, the "methyl" group adjacent to the amide function is locked in a permanent methylene bridge; thus it cannot interfere sterically with the interaction of the amide group with a repellent receptor site.

Only compounds 14 and 20 withstood 1 rinse period to provide protection against both mosquitoes; compound 9 was effective against *Ae. aegypti* after 1 rinse but was ineffective against *An. quadrimaculatus*. No compounds were effective after 2 rinse tests.

Many of the test chemicals have also shown promise as repellents against other species of biting fly. Schreck et al. (1977, 1978) reported them as highly effective against the stable fly, *Stomoxys calcitrans* (L.), and black flies (Simuliidae). Tests are being conducted against other insect species to establish the extent of broad spectrum repellency possessed by this group of promising repellents.

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