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TOPICAL MOSQUITO REPELLENTS VIII: SUBSTITUTED 2-THIO-4-THIAZOLIDINEONES AND 2,4-THIAZOLIDINEDIONES [1]

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ABSTRACT. 2-Thio-4-thiazolidineone and 2,4-thiazolidinedione derivatives with substituents in the 3- and 5-positions were synthesized and evaluated on human skin for repellency against female *Aedes aegypti* mosquitoes. In the 2-thio-4-thiazolidineone series, compounds with boiling points of approximately 95° C/0.5 mm Hg and, in the 2,4-thiazolidinedione series, compounds with boiling point ranges of 90 to 115° C/0.5 mm Hg exhibited the longest duration of repellency. 3-n-Hexyl-2,4-thiazolidinedione approaches N,N-diethyl-*m*-toluamide (deet) in duration of topical repellency.

INTRODUCTION

In recent years, there has been public controversy on the widespread use of chemical insecticides against mosquitoes and other insects for the control of vector-borne diseases. This is partly due to the persistence of insecticides such as DDT in the environment and to the fact that insects have developed resistance to many insecticides. Hence, the current interest in vector control centers on the use of new, less persistent insecticides and on the development of promising biological control methods. In addition to or instead of these control measures, topical insect repellents can give immediate protection to individuals engaged in military or civilian activities, especially in areas where total eradication of disease-carrying insects is not practical or feasible.

N,N-Diethyl-*m*-toluamide (deet), developed by USDA Entomology Research Laboratory (Florida), is the most important and effective topical mosquito repellent currently available, but it has limitations. Smith (1970) described the parameters for an ideal insect repellent; it is obvious that new and more effective insect repellents are needed. Recent publications from

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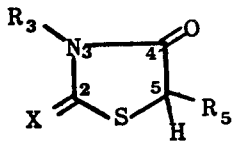
other investigators (Dremova et al., 1971, 1973; Potapov and Vladimirova, 1972, Potapov et al., 1973; Grothaus et al., 1974; Garner and Garson, 1973; Okoth, 1973; Anonymous, 1973) attest to the sustained interest in this area of research worldwide, especially in the USSR.

The continuing search in this laboratory for longer lasting topical mosquito repellents has led to detailed investigations of selected classes of chemical compounds, as reported by Johnson et al. (1967, 1968, 1974), Tsakotellis et al. (1971), and Gualtieri et al. (1972, 1973 a and b). Initially, leads were obtained by screening in an olfactometer a large number of compounds with various chemical functional groups having similar boiling or melting points, using deet (b.p. 100° C/0.5 mm Hg or ~300° C/760 mm Hg) as the standard reference, since an effective insect repellent should be volatile enough to form a repellent vapor barrier to the host-seeking mosquitoes. As a result of this screening, the 2-thio-4-thiazolidineone and 2,4-thiazolidinedione series of compounds were selected for study.

MATERIALS AND METHODS



X = S 2-thio-4-thiazolidineones (rhodanines)
X = O 2,4-thiazolidinediones
R_3 or R_5 = alkyl or aralkyl substituents

2-Thio-4-thiazolidineones. Most of the 2-thio-4-thiazolidineone compounds were synthesized following the procedures of Petlichna et al. (1961) and Minka (1963). The chemical structures of the products were ascertained by infrared (IR) and nuclear magnetic resonance (NMR) spectral data, by comparison of melting points or boiling points with literature references, or by elemental analyses.

The general synthetic procedure is the same as that used for 3-n-propyl-2-thio-4-thiazolidineone. To a mixture of 5.9 g (0.1 mole) of n-propylamine in 30 ml of water and 7.6 g (0.1 mole) of carbon disulfide was added dropwise 5.61 g (0.1 mole) of potassium hydroxide in 15 ml of water, with stirring and cooling in an ice-bath. The resulting mixture was stirred at room temperature for about 1.5 hr until all the CS_2 dissolved, after which was added a solution of 9.45 g (0.1 mole) of monochloroacetic acid in 20 ml of water neutralized by 6.91 g (0.05 mole) of anhydrous K_2CO_3, with cooling. The solution was stirred for about 1 hr, then reacted with 8.25 ml of conc. HCl, and finally poured into 40 ml of boiling conc. HCl. This mixture was heated to 90° C, cooled to room temperature, and extracted by one 100-ml and two 50-ml volumes of ether. The ether extracts were washed thoroughly with water, dried over anhydrous $MgSO_4$, and evacuated to give a yellow oil that distilled at 0.35 mm Hg and 100° C. The yield was 13.5 g of product, which could be purified further by chromatography using ether:petroleum ether (1:1) and silica gel.

Other 3-substituted 2-thio-4-thiazolidineones can be synthesized by using the appropriate amine—n-butyl-amine for the synthesis of 3-n-butyl-2-thio-4-thiazolidineone, for example. A similar modification for substituents in the 5-position can be effected by using alkyl homologs of alpha-bromoacetic acid, e.g., alpha-bromo-n-butyric acid (together with ethylamine) to yield 3,5-diethyl-2-thio-4-thiazolidineone.

2,4-Thiazolidinediones. All 3-substituted thiazolidinediones were synthesized by reacting an alkyl or aralkyl halide with the potassium salt of 2,4-thiazolidinedione, as reported by Lo and Shropshire (1957). Again, the chemical identity was ascertained by IR and NMR spectral data, by comparison with literature melting points or boiling points, or by elemental analyses. A typical synthesis, for 3-n-hexyl-2,4-thiazolidinedione, is as follows.

To a suspension of 4.65 g (0.03 mole)

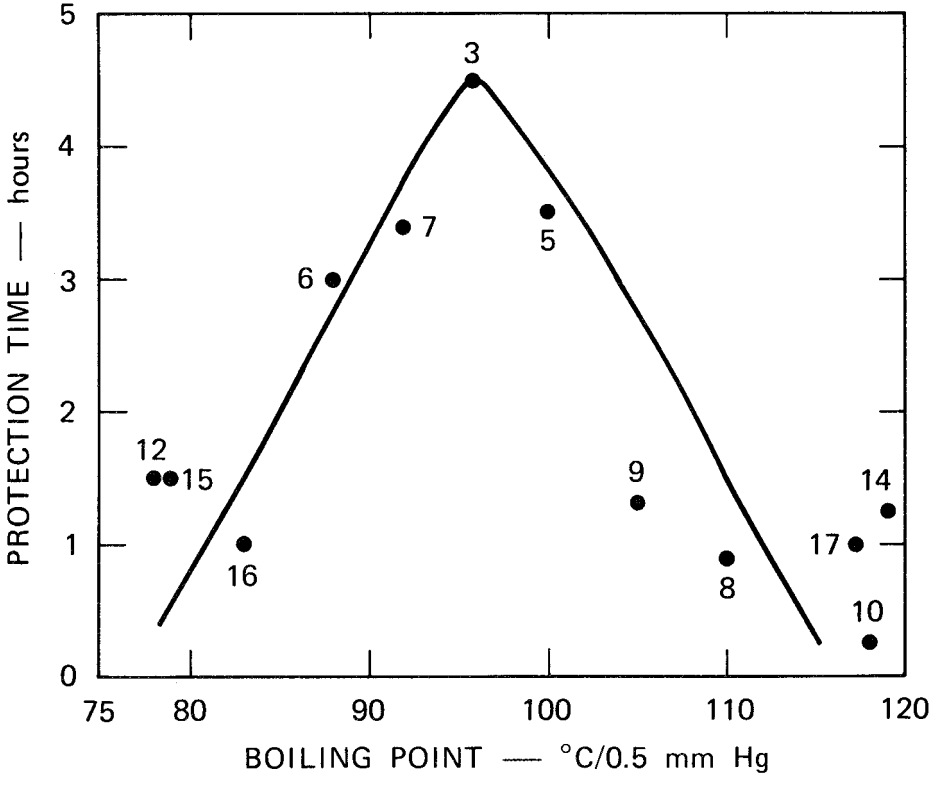
of the potassium salt of 2,4-thiazolidinedione in 15 ml of dimethylformamide was added slowly 4.95 g (0.03 mole) of n-hexyl bromide. The mixture was heated and refluxed on a steam bath for 4 hr and, after cooling, poured into 50 ml of water. The oil that separated was extracted with 50 ml and then 20 ml of chloroform. The chloroform solution was dried over anhydrous $MgSO_4$ and evacuated to give an oil that distilled at 0.25 mm Hg and 94° C, yielding 4.0 g of product.

Other 3-substituted 2,4-thiazolidinediones can be obtained by using the appropriate alkyl or aralkyl bromides, e.g., n-amyl bromide to produce 3-n-amyl-2,4-thiazolidinedione.

5-Substituted 2,4-thiazolidinediones were obtained from Dr. K. Folkers, Director, Biomedical Research Institute, University of Texas, Austin, Texas.

TEST PROCEDURE

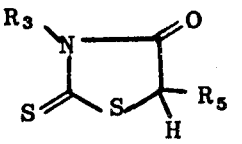
To determine the protection time of repellents, the test material (generally 10 or 20 mg) is dissolved in 1 ml of acetone. An area 5 in long and 2 in wide is marked on the ventral surface of the human forearm with ink. Small amounts of the dissolved material then are applied uniformly on the marked area with a medicine dropper, going over the surface several times (resulting in 1 mg/in^2 or 0.15 mg/cm^2 and



NOTE: Refer to Table I for compound identification.
Compound 3 is the 3-n-propyl derivative.

Fig. 1. Thio-4-thiazolidineone derivatives—volatility versus repellency at 0.30 mg/cm^2.

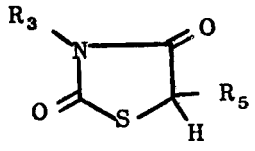
Table 1. Skin testing of 2-thio-4-thiazolidineones.



Graph number	Structure of compound R_3	Structure of compound R_5	Protection time [a] (hours on skin at 0.30 mg/cm²)	Boiling point ° C/mm Hg) or melting point (° C)	Analysis (percent) Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1	Methyl	H	1.0	mp 70	b	....	....	....	....	....
2	Ethyl	H	2.5	mp 37	b	....	....	....	....	....
3	n-Propyl	H	4.5	96/0.5	b	....	....	....	....	....
4	Isopropyl	H	1.0	mp 57	41.12%	5.18%	7.99%	40.91%	5.36%	8.24%
5	n-Butyl	H	3.5	100/0.5	44.42	5.86	7.40	44.25	5.65	7.62
6	sec-Butyl	H	3.0	88/0.5	44.42	5.86	7.40	44.25	5.97	7.57
7	Isobutyl	H	3.4	92/0.5	44.42	5.86	7.40	44.19	5.78	7.62
8	n-Amyl	H	0.25	110/0.5	47.26	6.44	6.89	47.08	6.49	7.07
9	iso-Amyl	H	1.0	105/0.5	47.26	6.44	6.89	47.46	6.69	7.11
10	n-Hexyl	H	0.25	118/0.5	49.73	6.96	6.44	49.96	7.05	6.40
11	Allyl	H	2.25	mp 47	c	....	....	....	....	....
12	Methyl	Methyl	1.5	78/0.5	37.42	4.38	8.69	36.97	4.62	8.57
13	Methyl	Ethyl	2.75	mp 56	41.42	5.18	7.99	40.87	5.26	8.10
14	Methyl	n-Hexyl	1.25	119/0.5	51.91	7.41	6.05	51.57	7.45	6.07
15	Ethyl	Methyl	1.5	79/0.5	41.12	5.18	7.99	40.87	5.25	7.89
16	Ethyl	Ethyl	1.0	83/0.5	44.42	5.86	7.40	44.30	5.68	7.33
17	Ethyl	n-Hexyl	1.0	117/0.5	53.84	7.80	5.71	53.84	7.95	5.84
18	H	n-Butyl	0.25	mp 82	44.42	5.86	7.40	44.34	5.89	7.67
19	H	n-Hexyl	1.0	mp 52	49.73	6.96	6.44	49.79	7.21	6.44
20	H	n-Decyl	0.25	mp 70	57.10	8.48	5.12	56.90	8.44	5.43
	deet		8.6	100/0.5						

[a] See Test Procedure.
[b] Obtained from Eastman Organic Chemicals.
[c] Obtained from Aldrich Chemical Company.

Table 2. Skin testing of 2,4-thiazolidinediones.



Graph number	Structure of compound R_3	Structure of compound R_5	Protection time [a] (hours on skin at 0.30 mg/cm²)	Boiling point ° C/mm Hg) or melting point (° C)	Analysis (percent) Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1	n-Butyl	H	1.5	80/0.5	48.53%	6.40%	8.09%	43.39%	6.18%	8.01%
2	n-Amyl	H	4.8	102/0.5	51.31	7.00	7.48	51.49	6.97	7.41
3	n-Hexyl	H	7.1	105/0.5	53.70	7.51	6.96	53.55	7.59	6.94
4	Isohexyl	H	2.5	86/0.5	53.70	7.51	6.96	53.53	7.78	6.91
5	n-Heptyl	H	4.3	115/0.5	55.78	7.96	6.51	55.82	8.13	6.76
6	n-Octyl	H	0.4	127/0.3	b	....	....	....	....	....
7	Benzyl	H	1.5	mp 60	c	....	....	....	....	....
8	o-Methylbenzyl	H	1.5	130/0.03	c	....	....	....	....	....
9	m-Methylbenzyl	H	1.1	mp 33	c	....	....	....	....	....
10	o-Chlorobenzyl	H	1.5	140/0.025	b	....	....	....	....	....
11	Ethylcarboxymethyl	H	0.25	mp 40	b	....	....	....	....	....
12	H	Ethyl	1.0	mp 58	41.37	4.86	9.65	41.41	5.12	9.71
13	H	Propyl	2.0	mp 37	45.27	5.70	8.80	43.50	5.85	8.54
14	H	Hexyl	0.25	mp 79	53.70	7.51	6.96	53.50	7.22	7.01
	deet		8.6	100/0.5						

[a] See Test Procedure.
[b] Reported by Lo and Shropshire (1957).
[c] Reported by Bradshire et al. (1956).

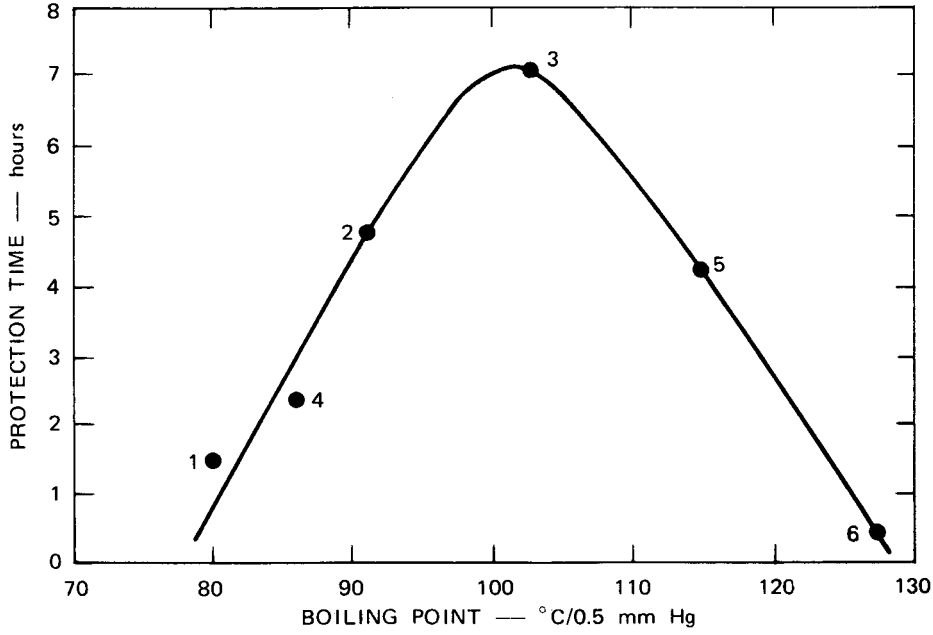
2 mg/in^2 or 0.30 mg/cm^2 concentration of repellent on the skin). Before protection against mosquito bites is tested, a long plastic sleeve is slipped over the entire forearm. The sleeve has a 5 x 2 in cutout, which is aligned with the marked area on the skin. A wire clamp attached around the arm holds the margins of the cutout along those of the coated area. The front end of the sleeve is sealed and serves as a glove.

For testing, the forearm is introduced through a cloth sleeve to a 1 x 1 x 1 ft cage containing 500±5% female *Aedes aegypti* (L.) mosquitoes. The repellent-coated area is exposed to mosquitoes for 3 min and then withdrawn. This procedure is repeated every 30 min until two bites are obtained. The duration from the time of application to the occurrence of two bites is counted as protection time. The mosquitoes used are 6 to 12 days old, mated, and have been fed 5% sucrose solution only. The adults are kept at 27° C and 60% relative humidity under a 12/12 light-and-dark regimen. All experiments are performed under these ambient conditions and are replicated at least two to four times.

RESULTS AND DISCUSSION

2-Thio-4-thiazolidineone. The compounds prepared were tested at 0.30 mg/cm^2 against yellow-fever mosquitoes, *A. aegypti* (see Table 1). The boiling points of those compounds that are liquids are corrected to 0.5 mm Hg for comparison of their relative volatility. When repellency is plotted against volatility (Figure 1), it is apparent that, generally, compounds with boiling points around 95° C/0.5 mm Hg have maximum repellency. Those compounds with much higher or lower boiling points in these series have less repellency, and the solids are also less repellent.

2,4-Thiazolidinediones. Following the



NOTE: Refer to Table II for compound identification.
Compound 3 is the 3-n-hexyl-2,4-thiazolidinedione.

Fig. 2. 2,4-Thiazolidinedione derivatives—volatility versus repellency at 0.30 mg/cm^2.

leads in the 2-thio-4-thiazolidineone series, we prepared a series of 2,4-thiazolidinediones having oxygen atoms in position 2 instead of sulfur atoms. Table 2 summarizes the results. Those compounds with alkyl substituents (1 to 6) are shown in Figure 2, in which repellency is plotted against volatility. As shown in previous studies, there is an optimal boiling point range in relation to repellency; in this series it is 90 to 115°/0.5 mm Hg. The benzyl derivatives exhibit low repellency and low volatility. Compounds 11 through 14 are solids and are not very repellent.

3-n-Propyl-2-thio-4-thiazolidineone is the best repellent in the 2-thio-4-thiazolidineone series, whereas 3-n-hexyl-2,4-thiazolidinedione is the best in the 2,4-thiazolidinedione series. The latter compound approaches DEET in its duration of repellency after topical application

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