

Topical Mosquito Repellents VII: Alkyl Triethylene Glycol Monoethers

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Abstract □ Normal and branched-chain aliphatic monoethers of triethylene glycol are effective topical mosquito repellents. In terms of duration of protection, they are generally superior to the corresponding diethylene glycol analogs and some are superior to diethyltoluamide. The *n*-heptyl monoether of triethylene glycol affords double the protection time of diethyltoluamide under controlled laboratory conditions and appears to be a useful new mosquito repellent.

Keyphrases □ Mosquito repellents, topical—synthesis, evaluation of alkyl triethylene glycol monoethers □ Repellents, mosquito, topical—synthesis, evaluation of alkyl triethylene glycol monoethers □ Monoethers, alkyl triethylene glycol—synthesis, evaluation as mosquito repellents □ Volatility, alkyl triethylene glycol monoethers—relationship to mosquito repellency □ Diethylene glycol versus triethylene glycol monoethers—mosquito repellency

The quest for improved topical mosquito repellent properties was pursued among benzyl ethers in previous studies (1, 2) with positive but not dramatic results. In the present study, nonaromatic polyethers derived from ethylene glycol were examined. The compounds were prepared *via* the sodio derivatives of diethylene or triethylene glycol and the appropriate alkyl halide or tosylate and were purified by vacuum distillation.

Products^{1,2} were evaluated topically on human subjects, using female *Aedes aegypti* mosquitos, as previously described (1).

EXPERIMENTAL³

Diethyltoluamide was obtained commercially⁴. Alkyl halides and alcohols corresponding to the R groups in Tables I and II were also obtained commercially and were used without further purification. Final products were purified and boiling points were determined by vacuum distillation using Vigreux columns.

Preparation of Monoalkyl Triethylene Glycol Ethers (Table I) from Alkyl Halide (Method A)—An ice-cooled, mechanically stirred, three-necked, 2-liter, round-bottom flask, fitted with a powder funnel and a gas inlet allowing passage of a slow stream of nitrogen, was charged with 180 ml of triethylene glycol. Sodium hydride (57% in oil, 13.0 g, 0.13 mole) was washed of its oil by swirling with 2 × 30 ml of ether and decanting. The hydride was then added in portions. After 2 hr, the ice bath was removed and the mixture was stirred for 2 hr on a steam bath.

To this stirred dark mixture was added 0.23 mole of the alkyl halide. After 20 hr, the opaque mixture was cooled, diluted with 800 ml of water, and extracted with methylene chloride (4 × 100 ml). Sodium chloride was used to help break emulsions. The combined organic layers were washed with water (2 × 200 ml), dried (anhydrous magnesium sulfate), and rotary evaporated. The clear

oil was fractionated *in vacuo* through a Vigreux column.

Preparation of Monoalkyl Triethylene Glycol Ethers (Table I) from Tosylate (Method B)—*Preparation of Tosylate*—The alcohol (0.08 mole) was dissolved in 130 ml of dry pyridine in a 250-ml erlenmeyer flask and stirred in an ice bath while *p*-toluenesulfonyl chloride (26 g, 0.14 mole) was added in several portions. After stirring for 1 hr the solution was placed in a refrigerator (−5°) overnight.

The deep-red mixture was added to 600 ml of ice water, stirred for 5 min, and extracted with 2 × 100 ml of ligroin. The combined organic layers were washed free of pyridine with 3 *N* HCl (16 ml) and ice water (pH 3–4), then washed with 50 ml of ice water, dried with anhydrous magnesium sulfate, and evaporated *in vacuo* to yield a red oil in 99% yield. The IR spectra showed tosylate bands at 6.21 and 8.60 μ m.

Alkylation of Triethylene Glycol—Triethylene glycol (180 ml) was heated on a steam bath with 1.74 g (76 mmoles, 5% excess) of sodium spheres for 1 hr in a 250-ml flask equipped with a drying tube. Gas was evolved slowly, and the sodium was dissolved to yield a clear yellow solution. The alkyl tosylate (64 mmoles) was added, and the mixture was stirred at room temperature for 3 days.

The clear, light-brown mixture was added to 1 liter of ice and water and extracted with methylene chloride or ether (3 × 200 ml). Emulsions were usually encountered and were occasionally broken by acidifying the alkaline mixture with 3 *N* HCl. The combined organic layers were washed with water (3 × 200 ml), dried (anhydrous magnesium sulfate), evaporated *in vacuo* to a yellow oil (95% crude), and distilled through a Vigreux column *in vacuo*.

Repellency evaluations were conducted *via* both skin and cloth tests, utilizing female *A. aegypti*.

Tests on Skin—Compounds were uniformly applied in ethanol to an exposed area of the forearm of a human subject as described previously (1) (Tables I–III).

Tests on Cloth¹—The methodology was described previously (3) except that the rate of cloth treatment was reduced by one-half until three bites per minute were received at the lowest dose. Diethyltoluamide and dimethyl phthalate were tested concurrently as standards (Table IV).

Other Tests on Skin²—The test methodology was similar to that used under *Tests on Skin* (Tables I and II). Results are given in Table V.

RESULTS AND DISCUSSION

A far more restricted volatility–repellency relationship was apparent in this series (Tables I and II) as compared with those previously studied (1–3). Nonetheless, maximum duration of protection in two application rates to skin was observed with Compounds I-2 and I-3 (Table I), whose volatility corresponded to boiling points in the range of 120–130°/0.5 mm Hg. They outperformed the standard, diethyltoluamide (I-14), by a substantial margin. No definite reason can be given for the comparatively poorer performance of other members of the series whose volatility would appear to be close to this optimum range, *e.g.*, Compounds I-9–I-11 (Table I); however, it is possible that the volatility of these compounds deviates from the optimum at skin temperature.

In any event, the findings suggest that maximum duration in this series is associated with C₆–C₇ alkyl ethers. Among the C₈ ethers studied, it appears that the straight-chain compound (I-4) is superior to branched isomers (I-6 and I-11) and the cyclic analog (I-12). The same generalization seems applicable to the C₇ series (I-3 and I-7) and the C₉ series (I-5, I-9, and I-10). The repellencies of the diethylene glycol analogs (Table II) were substantially infe-

¹ Several compounds were also subjected to independent evaluation on cloth at the Gainesville laboratories of the U.S. Department of Agriculture.

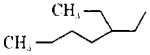
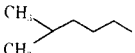
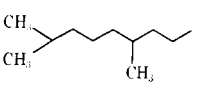
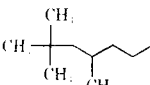
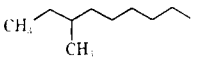
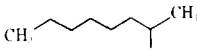
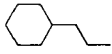
² Two compounds were subjected to further independent evaluation at the Letterman Army Institute of Research.

³ Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, Stanford University, Stanford, Calif.

⁴ Eastman Organic Chemicals

Table I—Alkyl Triethylene Glycol Monoethers

R(OCH₂CH₂)₃OH

Compound	R	Yield, %	Formula	Analysis, %		Boiling Point (mm)	Repellency, hr ^a	
				Calc.	Found		0.15 mg/cm ²	0.31 mg/cm ²
I-1	<i>n</i> -C ₃ H ₁₁	50 ^b	C ₁₁ H ₂₄ O ₄	C 59.97 H 10.98	59.71 11.24	111° (0.5)	5.8 (2)	9.0 (5)
I-2	<i>n</i> -C ₆ H ₁₃	67 ^b	C ₁₂ H ₂₆ O ₄	C 61.50 H 11.18	61.74 11.41	122° (0.4) ^c	5.7 (30)	10.0 (30)
I-3	<i>n</i> -C ₇ H ₁₅	54 ^b	C ₁₃ H ₂₈ O ₄	C 62.87 H 11.37	63.07 11.70	128° (0.4)	10.6 (4)	13.0 (4)
I-4	<i>n</i> -C ₈ H ₁₇	71 ^b	C ₁₄ H ₃₀ O ₄	C 64.08 H 11.53	64.08 11.50	139° (0.45)	—	8.1 (11)
I-5	<i>n</i> -C ₉ H ₁₉	60 ^b	C ₁₅ H ₃₂ O ₄	C 65.18 H 11.67	65.38 11.68	153° (0.65)	2.6 (4)	9.8 (5)
I-6		33 ^b	C ₁₄ H ₃₀ O ₄	C 64.08 H 11.53	64.04 11.63	120° (0.13)	4.7 (12)	6.4 (9)
I-7		76 ^b	C ₁₂ H ₂₆ O ₄	C 61.50 H 11.18	61.38 11.12	149° (3.25) ^d	4.3 (3)	7.0 (3)
I-8		55 ^b	C ₁₆ H ₃₄ O ₄	C 66.16 H 11.80	65.78 12.06	169° (2.0) ^c	1.3 (3)	3.3 (3)
I-9		59 ^b	C ₁₅ H ₃₂ O ₄	C 65.18 H 11.67	65.00 11.94	130° (0.35)	1.3 (4)	2.8 (3)
I-10		90 ^f	C ₁₅ H ₃₂ O ₄	C 65.18 H 11.67	64.87 11.98	140° (0.7)	1.0 (3)	1.8 (2)
I-11		50 ^f	C ₁₄ H ₃₀ O ₄	C 64.08 H 11.53	63.73 11.69	130° (0.5)	4.5 (4)	4.3 (3)
I-12		58 ^f	C ₁₄ H ₂₈ O ₄	C 64.58 H 10.84	64.54 10.77	134° (0.3)	1.1 (3)	4.8 (2)
I-13	C ₆ H ₅ CH ₂	30 ^g	C ₁₃ H ₂₀ O ₄	C 64.98 H 8.39	64.74 8.24	148° (0.55)	—	0.25 (1)
I-14	Diethyltoluamide	—	—			100° (0.5)	3.4 (11)	6.9 (12)

^a Number of determinations is given in parentheses. ^b Method A: prepared from bromide. ^c Lit. (4) 153–154° (5 mm). ^d About 118°/0.5 mm. ^e About 145°/0.5 mm. ^f Method B: prepared from tosylate. ^g Method A: prepared from chloride.

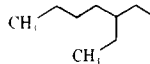
rior to those of the corresponding triethylene glycol ethers and, in both series, the benzyl analogs (I-13 and II-5) were inferior to the aliphatic compounds.

To obtain a more direct comparison, independent of day-to-day variations in insect avidity, topical repellency was determined simultaneously for diethylene and triethylene glycol ethers in paired

tests of compounds with identical *O*-alkyl substituents (Table III). The triethylene glycol ethers were clearly superior when the R group was hexyl or heptyl. However, superiority was reversed in the *n*-octyl compounds, and the 2-ethylhexyl derivatives showed approximately equal duration. It is assumed that the increased polarity of the triethylene glycol series over that of the diethylene

Table II—Alkyl Diethylene Glycol Monoethers

R(OCH₂CH₂)₂OH

Compound	R	Yield, %	Formula	Analysis, %		Boiling Point (mm)	Repellency, hr ^a	
				Calc.	Found		0.15 mg/cm ²	0.31 mg/cm ²
II-1	<i>n</i> -C ₆ H ₁₃	~80 ^b	C ₁₀ H ₂₂ O ₃	C 63.12 H 11.65	63.21 11.57	82° (0.55)	1.8 (2)	2.8 (2)
II-2	<i>n</i> -C ₇ H ₁₅	70.5 ^b	C ₁₁ H ₂₄ O ₃	C 64.66 H 11.84	64.65 11.56	93° (1.6)	—	5.9 (10)
II-3	<i>n</i> -C ₈ H ₁₇	43 ^b	C ₁₂ H ₂₆ O ₃	C 66.01 H 12.00	65.78 12.03	104.5° (0.45)	—	4.5 (2)
II-4		32 ^b	C ₁₂ H ₂₆ O ₃	C 66.01 H 12.00	65.83 11.96	98° (0.5)	3.5 (3)	4.9 (7)
II-5	C ₆ H ₅ CH ₂	27 ^c	C ₁₁ H ₁₆ O ₃	C 67.32 H 8.22	67.19 8.32	117° (0.45)	—	1.0 (1)
II-6	(CH ₃ CH ₂ O) ₂ CHCH ₂	22 ^b	C ₁₀ H ₂₂ O ₃	C 54.03 H 9.98	54.02 9.92	119° (1.2) ^d	1.0 (2)	1.5 (2)

^a Number of determinations is given in parentheses. ^b Method A: prepared from bromide and diethylene glycol. ^c Method A: prepared from chloride and diethylene glycol. ^d About 100°/0.5 mm.

Table III—Dry Protection Times^a of Monoalkyl Ethers of Diethylene Glycol ($n = 2$) versus Triethylene Glycol ($n = 3$)

Compound	Mean Protection Time, hr \pm SD			
	<i>n</i> -Hexyl	<i>n</i> -Heptyl	<i>n</i> -Octyl	2-Ethylhexyl
R(OCH ₂ CH ₂) ₂ OH	3.6 \pm 0.90	5.9 \pm 0.95	11.0 \pm 3.95	4.0 \pm 0.88
R(OCH ₂ CH ₂) ₃ OH	12.9 \pm 2.77	11.6 \pm 3.65	7.5 \pm 5.03	5.0 \pm 2.04

^a Results are means of 10 determinations in which diethylene and triethylene glycol ethers of identical R group were paired (same test subject). Compounds were applied at 0.31 mg/cm².

Table IV—Comparative Repellent Evaluations^a

Compound ^b	Minimum Effective Dose after Indicated Drying Time, mg/cm ²	
	15 min	24 hr
I-1	0.063	0.25
I-2	0.032	0.25
I-3	0.016	0.125
I-4	0.016	0.25
I-5	0.032	0.25
I-7	0.032	0.125
I-14	0.008	0.25
Dimethyl phthalate (standard)	0.008	0.5

^a Tests conducted by personnel at the Insects Affecting Man Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Gainesville, Fla. ^b See Table I.

glycols of similar volatility should present durational and toxicological advantages in terms of reduced percutaneous absorption rates.

Results of minimum effective dose (MED) tests (Table IV) generally correlated with the results of topical duration tests. Both at 15 min and 24 hr after application, I-3 exhibited minimum MED values. Although these values were not as low at 15 min as those obtained for diethyltoluamide and dimethyl phthalate, I-3 was superior to both standards in the 24-hr test.

Table V—Repellent Evaluations^a

Compound ^b	Repellency ^c , hr \pm SD	Number of Exposures
I-2	8.50 \pm 4.7	12
I-3	16.75 \pm 5.6	8
I-14	6.68 \pm 0.81	128
2-Ethylhexanediol	3.40 \pm 0.5	40

^a Tests conducted by personnel at Letterman Army Institute of Research using 200 female *A. aegypti* in a 1.25-ft³ cage (5). ^b See Table I; compounds were applied to forearms of human volunteers at the rate of 0.31 mg/cm². ^c Mean dry protection times (prevention of biting).

The superiority of I-3 in Table I was confirmed by tests conducted independently² (Table V). It provided more than double the protection time afforded by diethyltoluamide to a group of volunteers under controlled laboratory conditions. Preliminary results of field tests indicate that the moderate laboratory superiority of I-2 can be nullified by conditions of heavy sweating and high insect population density. Field tests have not yet been conducted with I-3 and I-4.

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