mouse brain (6), and optimum anesthetic potency to mice (7) of a series of 26 ethers administered in vapor phase was associated with $\log P_0 = 2.35$. Our result is consistent with these observations.

The inactivity of the 4-hydroxy derivative is difficult to explain on the basis of lipophilicity and the electronic nature of the OH group. Its predicted activity according to Eq. 3 is 3.29. Since the compound showed no activity, it must not be accessible to the CNS. This could be due to metabolism but further work would be necessary to substantiate this.

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Topical Mosquito Repellents VI: Sulfonamides and Quinoline-4-carboxylic Acid Derivatives

F. GUALTIERI*, P. TSAKOTELLIS†, W. SKINNER▲, H. JOHNSON, D. SKIDMORE‡, and H. MAIBACH‡

Abstract □ Certain sulfonamides derived from butanesulfonic acid are repellent to female *Aedes aegypti* mosquitoes. Exploration of the structure–activity relations revealed that the boiling point is the most important factor controlling duration of activity as topical repellents. Quinoline-4-carboxylic acid derivatives were explored for their repellency, and amides were found less active than were esters, primarily due to their low volatility.

Keyphrases □ Mosquito repellents, topical—synthesis, evaluation of butane sulfonamides and quinoline-4-carboxylic acid derivatives □ Repellents, mosquito, topical—synthesis, evaluation of butane sulfonamides and quinoline-4-carboxylic acid derivatives □ Quinoline-4-carboxylic acid derivatives—synthesis, evaluated as topical mosquito repellents □ Sulfonamides, butane—synthesis, evaluated as topical mosquito repellents □ Volatility, quinoline-4-carboxylic acid derivatives—relationship to mosquito repellency

In 1967, Pervomaisky *et al.* (1) reported that certain butane sulfonamides were effective mosquito repellents. The most active of these was reported to be the hexamethyleneimino derivative. This compound and several other analogs were synthesized in the present study for evaluation as topical repellents for *Aedes aegypti* mosquitoes (Table I). The syntheses were straightforward, utilizing *n*-butanesulfonyl chloride in benzene with an excess of the amine. The products were purified by vacuum distillation.

All derivatives were evaluated topically on human subjects as previously described (2). None of the analogs of Compound 1 improved on its activity as a mosquito repellent, although Compounds 3 and 4 had similar activities. As in compounds previously studied as repellents, duration of repellency in a series is a function of the boiling point of the compounds. In this series, maximum duration seems to be achieved with boiling points of 120–130°/0.5 mm. whereas *N,N*-diethyl-*m*-toluamide, which lasts longer, boils at 100°/0.5 mm.

Another interesting lead to mosquito repellents was reported in 1968 (3, 4). These investigators found that certain cinchoninic acid esters were highly repellent. These compounds were evaluated in the present study and several amide analogs were synthesized (Table II). None of the amides exhibited any degree of repellency, probably due to the fact that volatility is reduced too much going from the esters to the amides.

Four of the sulfonamides were evaluated on cloth by the U. S. Department of Agriculture (Table III). The superiority of Compound 1 in these tests over dimethyl phthalate is interesting.

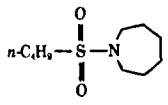
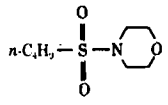
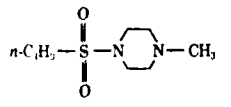
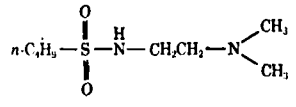
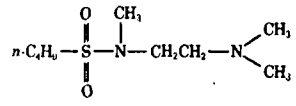
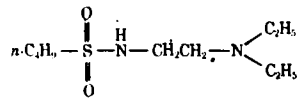
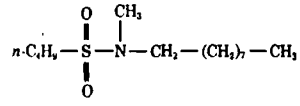
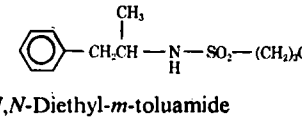
EXPERIMENTAL

n-Butyl Sulfonamides—A solution of *n*-butanesulfonyl chloride (0.03 mole) in anhydrous benzene was slowly added to a solution of the amine (0.06 mole) in anhydrous benzene with cooling and stirring. The solution was then heated to reflux for 1 hr. and, after cooling, the benzene solution was washed with water and dried with sodium sulfate. The oil remaining after evaporation of the solvent was distilled through a short Vigreux column.

Quinoline-4-carboxylic Acid Pyrrolidine Amide—Quinoline-4-carboxylic acid chloride (0.1 mole) (7) was added in small portions to a solution of 0.25 mole of pyrrolidine in anhydrous benzene. After 1 hr. at room temperature, the mixture was heated to reflux for 1 hr. and then cooled, and the benzene solution was washed with water. After drying with sodium sulfate and evaporation of the solvent, the oil was distilled *in vacuo*.

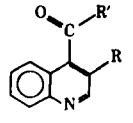
Biological Evaluation: Cloth Tests—Fifty milligrams of the test material is placed in a 2-dram vial to which 0.75 ml. of acetone or other solvent is added. When the chemical is thoroughly dissolved, a 50-cm.^{2} (5 × 10-cm.) piece of muslin bandage is rolled, placed in

Table I—Sulfonamides

Compound Number	Structure	Yield, %	Formula	Analysis, % Calc.	Analysis, % Found	Boiling Point (0.5 mm.)	Repellency, hr. (0.15 mg./cm.²)	Repellency, hr. (0.35 mg./cm.²)
1		—[a]	$C_{10}H_{21}NO_3S$	—[a]	—[a]	130°	1	2
2		67	$C_8H_{17}NO_3S$	C 46.45 H 8.26 N 6.75 S 15.47	46.16 8.19 6.62 15.54	140°	—	1
3		47	$C_9H_{20}N_2O_3S$[b]	C 40.09 H 5.16 N 15.58 S 7.13	40.13 5.02 15.51 7.02	124°	—	2
4		63	$C_8H_{20}N_2O_2S$[b]	C 38.44 H 5.30 N 16.01 S 7.33	38.34 5.26 15.76 7.54	130°	1	—
5		72	$C_9H_{22}N_2O_2S$[b]	C 39.91 H 5.58 N 15.51 S 7.10	40.05 5.52 15.72 7.25	115°	—	1
6		34	$C_{10}H_{24}N_2O_2S$[b]	C 42.58 H 6.09 N 14.61 S 6.69	42.61 6.02 14.49 6.61	147°	—	1
7		63	$C_{14}H_{31}NO_2S$	C 59.23 H 10.81 N 5.28	59.28 11.10 5.32	145°	—	0.25
8		96	$C_{13}H_{31}NO_2S$	C 60.90 H 8.35 N 5.94	61.14 8.29 5.48	170°	—	0.25
9	*N,N*-Diethyl-*m*-toluamide					100°	1–2	3–5

[a] See *Reference 1*. [b] Analyzed as picrate salt.

Table II—Amides and Esters of Quinoline-4-carboxylic Acid



Compound Number	R	R′	Boiling Point (mm.)	Repellency, hr. (0.35 mg./cm.²)
10	H	$N(C_2H_5)_2$	145° (0.2)[a]	0.25
11	H		175° (0.2)[b]	0.25
12	H	OC_2H_5	109° (0.25)[c]	0.25
N,N-Diethyl-*m*-toluamide				2–3
13	CH_3	OC_2H_5	143° (1.0)[d]	6[e]
14	CH_3	O-*n*-C_3H_7	149° (1.0)[d]	5[e]
15	CH_3	O-*n*-C_4H_9	163° (1.0)[d]	6.5[e]
16	C_2H_5	OC_2H_5	155° (1.0)[d]	5.5[e]
N,N-Diethyl-*m*-toluamide			100° (0.5)	10[e]

[a] See *Reference 5*. [b] Synthesized in 87% yield. Calc. for C, H, N: 74.31, 6.24, 12.38. Found: 74.26, 6.47, 12.30. [c] See *Reference 6*. [d] These compounds were obtained from Dr. G. H. Yeoman, Astra-Hewlett, Ltd., Veterinary Research Station, Wheathampstead, Herts, England. [e] Evaluated at 1.75 mg./cm.².

the vial, and mixed with the solution, and the vial is sealed until the chemicals are to be tested. The rate of cloth treatment is 1.0 mg./cm.². After treatment the cloths are kept in the vials in a refrigerator for at least 24 hr.

At the start of a test, vials are removed from the refrigerator and allowed to warm to room temperature. The cloth is then removed from the vial and stapled over a 5 × 9-cm. rectangular opening cut in a 12.7 × 20.3-cm. (5 × 8-in.) file card. The cloth is allowed to dry for 15 min. before testing.

The subject testing the candidate materials covers his arms with a woman's nylon stocking and wears a rubber glove over his hand and wrist to protect against bites. The card and attached cloth patch are then taped over the nylon-covered forearm so that only the treated cloth allows access to the skin by the mosquitoes. The arm is then exposed to a stock cage of *A. aegypti* mosquitoes (approximately 1500) for 1 min. Two or more bites through the treated cloth in 1 min. denotes failure of the chemical. If the chemical does not fail, it is stored at room temperature and retested in 24 hr.

Two standard repellents are tested with each group of candidate material: dimethyl phthalate at the rate of 1.0, 0.5, 0.25, and 0.125 mg./cm.² and diethyltoluamide at 0.25 and 0.125 mg./cm.².

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Table III—Repellent Evaluations on Cloth

Compound	Rate of Application on Cloth, mg./cm.²	Number of Bites Obtained at Indicated Hour 0	24	96	144	192
1	1.0	0	0	0	0	0
2	1.0	30	—	—	—	—
3	1.0	35	—	—	—	—
4	1.0	25	—	—	—	—
Dimethyl phthalate	1.0	0	0	10	—	—
	0.5	0	20	—	—	—
	0.25	2	10	—	—	—
N,N-Diethyl-*m*-toluamide	0.25	0	10	—	—	—
	0.125	0	25	—	—	—

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Comparison of Theoretical Equations for Potential Energy of Electrostatic Repulsion of Colloidal Particles at Constant Surface Charge

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Abstract □ Recently, derived and relatively simple expressions for the energy of electrostatic repulsion between flat plates and spheres at constant surface charge were compared with the more rigorous expressions of Jones and Levine and of Müller. They are quantitative of the electrostatic barrier to the collision of colloidal particles in electrolyte solutions within the limitation of small surface potentials, $\psi_0 < 25$ mv. They are also useful in the general approximation of colloidal stability of most practical systems, despite the limitations on the validity of the expression at higher surface potentials.

Keyphrases □ Colloidal particles, potential energy of electrostatic repulsion, at constant surface charge—comparison and discussion of simple and complex equations □ Surface potential—comparison of equations for the potential energy of electrostatic repulsion of colloidal particles □ Electrostatic barrier—discussion of several equations for determining potential energy of electrostatic repulsion of colloidal particles at constant surface charge

In those dispersed systems in which the primary barrier to flocculation is electrical, the classical theory of the repulsive interaction of overlapping electrical double layers between two particles combined with the attractive interaction due to dispersion forces is used. Moreover, the usual model employed for the repulsive energy requires that the surface potential remains constant during the collision of particles, although the model of constant surface charge, in which case the surface potential increases during the encounter, is applicable in most dispersed systems (1).

Frens *et al.* (2, 3) showed that the collision of silver iodide colloidal particles in aqueous electrolyte solutions was more appropriately explained by the constant surface charge condition. They employed the exact solution of the Poisson–Boltzmann equation in the form of elliptical integrals. Recently, while examining the question of the surface potential or charge remaining constant during the mutual approach of particles, Jones and Levine (4) derived approximate expressions in series form and compared their equations

Table I—Comparison of the Potential Energy of Electrostatic Repulsion Calculated from Various Equations for the Constant Surface Charge Model at Various Interplate Distances

$Z\eta_0$	$\frac{\kappa}{16nkT} V_R$ at $2\kappa d = 1$: Müller (5)	Jones and Levine (4)	Equation 1	$\frac{\kappa}{16nkT} V_R$ at $2\kappa d = 2$: Müller (5)	Jones and Levine (4)	Equation 1
0.5	0.0330	0.0302	0.0364	0.0095	0.0094	0.0098
1.0	0.1108	0.1087	0.1455	0.0347	0.0347	0.0391
2.0	0.3219	0.3213	0.5820	0.1106	0.1099	0.1565
4.0	0.8087	0.8567	2.3280	0.2765	0.2651	0.6261