[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

INSECT REPELLENTS. III. N,N-DIETHYLAMIDES[1]

E. T. McCABE, W. F. BARTHEL, S. I. GERTLER, AND S. A. HALL

Received October 30, 1953

If a compound is chosen at random from a list of compounds that have exhibited high repellency against insects, its chances are surprisingly small of surviving subsequent rigid suitability and pharmacology tests that are required before it may finally be recommended for use on humans (1). It is therefore necessary to synthesize a large variety of candidate repellents from which to choose. In an extensive screening program conducted by the Bureau of Entomology and Plant Quarantine at Orlando, Fla., to discover superior repellents for use against mosquitoes, ticks, and mites (2), considerable information has been amassed to enable the chemist to attempt correlations of structure with repellent activity. Although conclusions on structural correlation can be drawn only with caution, there are certain general principles that seem to hold true. For example, among esters (3) the chances of finding repellent compounds are very much greater than among hydrocarbons. Furthermore, of all the structural groups thus far studied, certain diols and the N,N-dialkylamides, especially diethylamides furnish very promising leads as a source of mosquito repellents.

Two diols that are very effective mosquito repellents are 2-ethyl-1,3-hexanediol and 2-butyl-2-ethyl-1,3-propanediol; they are also safe and suitable for use on human skin or for impregnating clothing. Three diethylamides have survived the extensive and rigorous tests leading to permissible use by the military services —namely, propyl N,N-diethylsuccinamate (4), *o*-chloro-N,N-diethylbenzamide (5), and *o*-ethoxy-N,N-diethylbenzamide (6). The last-named compound is one that resulted from the present study. The first diethylamide found to exhibit marked repellency to mosquitoes was N,N-diethylbenzamide, patented by Gertler (7). This repellent was subsequently found to be somewhat irritating to human skin and hence was barred from use. A series of diethylamides, many of them monoesters of dibasic acids (especially succinic acid), were prepared by Drake and co-workers (8) during World War II, under contract with the Office of Scientific Research and Development. A high proportion of these monoester dialkylamides exhibited mosquito repellency and were patented by Drake, Shenk and Eaker (4) for this purpose. They (9) also made a series of N,N-dialkyl-β-hydroxyamides for testing as insect repellents.

The diethylamides tested at Orlando (2) have been grouped according to the structural similarity of the acyl group. These compounds represent the background information for the new diethylamides prepared in the study reported herein and are as follows:

[1] This work was conducted under funds allotted by the Department of the Army to the Bureau of Entomology and Plant Quarantine.

N,N-DIETHYLAMIDE	MOSQUITO REPELLENCY	
	On Skin	On Cloth
FROM ALIPHATIC ACIDS		
Formic	Neg.	—
Acetic	Neg.	—
Propionic	—	Neg.
Butyric	++	—
Lauric	Neg.	—
10-Hendecenoic (or undecylenic)	+++	+++
FROM KETO, HYDROXY, OR ALKOXY ACIDS		
Acetoacetic	+	+++
Levulinic	++	—
Levulinic, ketal with ethylene glycol	—	+++
Acetic, α-butoxy-	—	+++
Caproic, 3-hydroxy-3-methyl-	—	+++
FROM DIBASIC ACIDS (MONOESTERS)		
Succinic, (monodiethylamide)	—	+
Succinic, monoethyl ester	+++	+++
Succinic, monopropyl ester	++++	+++
Succinic, monoisopropyl ester	+++	+++
Succinic, monobutyl ester	Neg.	—
Succinic, monoisobutyl ester	Neg.	—
Succinic, mono-*sec*-butyl ester	++++	+++
Succinic, monoallyl ester	Neg.	—
Succinic, monomethoxyethyl ester	Neg.	—
Glutaric, monomethyl ester	++++	+++
Glutaric, monoethyl ester	++	—
Glutaric, monopropyl ester	+	+++
Glutaric, α-hydroxy-α-methyl-, α-lactone	+	+++
Adipic, monomethyl ester	+	+++
Adipic, monoethyl ester	+++	+++
Adipic, monoisopropyl ester	+	+++
Maleic, monoethyl ester	+++	+++
FROM AROMATIC AND CYCLIC ACIDS		
Benzoic	+++	+++
Benzoic, *o*-chloro-	++++	—
Benzoic, *m*-nitro-	+	+
Benzoic, *p*-nitro-	—	Neg.
Phenylacetic	Neg.	—
Hydracrylic, β-phenyl-	+	—
Cinnamic	—	Neg.
Phthalic, Δ^4-tetrahydro-, monomethyl ester	++	—
Phthalic, Δ^4-tetrahydro-, monoethyl ester	+	+++
Furoic	+	+++
Furanacrylic	++	+++
Acetic, 1-hydroxycyclohexane-	+	+++
Acetic, α-cyclohexoxy-	+++	+++
Nicotinic	—	Neg.

These ratings are indicated as follows: ++++, excellent; +++, very good; ++, good; +, fair; neg., little activity.

In this study we prepared diethylamides, chiefly of aromatic acids (Table I). The ring-substituted diethylbenzamides yielded a high percentage of repellents. Exceptions were noted when the ring-substituent was hydroxy, alkoxy higher than ethoxy, di- or tri-alkoxy, or di-halogen. Among the alkoxy-substituted diethylbenzamides the *ortho* position seems to favor repellency but not the *para* position. On the other hand, among the alkyl-substituted diethylbenzamides, all of which exhibited appreciable repellency, the position of the substituent in the ring appeared to have no decisive effect on repellent activity.

None of these compounds are recommended for general use as repellents, as the necessary pharmacological data relating to their practical use have not been obtained.

Acknowledgment. The authors wish to thank Carroll N. Smith, I. H. Gilbert, and others of the staff of the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine for conducting the insect repellency tests. Detailed entomological results on the compounds described in this paper will be reported by members of the Orlando laboratory staff.

EXPERIMENTAL

Preparation of N,N-diethylamides. The organic acid (for example, toluic or cyclohexanecarboxylic acid) was mixed with a 50% excess of purified thionyl chloride and refluxed on the steam-bath for 1 to 8 hours, or until hydrogen chloride evolution ceased. Excess thionyl chloride was removed at the water pump. The acid chloride residue was vacuum-distilled; if a solid it was recrystallized from petroleum ether. In the case of hydroxy acids (hydroxybenzoic or vanillic acid) the hydroxy group was protected by acetylation with acetic anhydride before being treated with thionyl chloride. The acetyl group was finally removed by mild alkaline hydrolysis.

The acid chloride (0.1 mole) was added slowly, by means of a dropping-funnel, to a cooled solution of dry diethylamine (0.2 mole) in 100 ml. of dry ether. The reaction mixture was stirred with a magnetic stirrer during the addition and continued for 1 hour at room temperature after all the acid chloride had been added. Enough cold water was then added to dissolve the precipitated diethylamine hydrochloride. The organic layer was separated and washed successively with 100-ml. portions of 5% hydrochloric acid solution, water, 5% sodium hydroxide solution, water, and finally with a saturated solution of sodium chloride. The ether extract was filtered through a plug of dried cotton, the ether was removed at the water-pump, and the residual diethylamide was purified by vacuum-distillation. Yields were generally high. A few exceptions are noted in Table I.

SUMMARY

Thirty-three N,N-diethylamides, chiefly of aromatic acids, were prepared for testing as insect repellents. The most promising mosquito repellents of this series were derived from the ring-substituted benzoic acids. Some structural correlations are discussed.

BELTSVILLE, MARYLAND

Table I follows on pages 496 and 497.

TABLE I

N,N-Diethylamides $RCON(C_2H_5)_2$

Derived from (Acid)	Yield,[b] %	n_D^{25}	B.P. °C./mm.	M.P. °C.	Analyses,[a] C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	Mosquito repellency On Skin	Mosquito repellency On Cloth
Senecioic	82	1.4702	115/20[c]	—	—	—	—	—	—	—	—	Neg.
Sorbic	74	1.5244	145–147/16	—	71.81	70.53	10.25	10.03	8.38	8.78	—	++
o-Toluic	90	—	105/1.0[d]	49–50	75.35	75.65	8.96	8.58	7.32	7.52	++++	+++
m-Toluic	94	1.5206	111/1.0[e]	—	—	—	—	—	—	—	++++	++++
p-Toluic	94	—	110/1.0[f]	53.5–55.5	—	—	—	—	—	—	++++	++++
Benzoic, *p*-isopropyl	65	1.5151	106–108/0.1	—	76.67	75.97	9.65	9.42	6.39	6.78	—	++++
Benzoic, *m*-hydroxy-	50	—	—	80[g]	—	—	—	—	—	—	—	Neg.
Benzoic, *p*-hydroxy-	51	—	—	120[h]	—	—	—	—	—	—	—	Neg.
Vanillic	60	—	—	98–99	64.55	64.55	7.67	7.82	6.27	6.13	—	Neg.
Benzoic, *o*-methoxy-	87	—	100–104/1.0[i]	36–38[i]	—	—	—	—	—	—	—	+++
Anisic	82	—	138/1.3[j]	48[j]	—	—	—	—	—	—	—	Neg.
o-Veratric	85	1.5225	120/0.2	—	65.80	65.39	8.07	8.29	5.90	5.99	—	++
Benzoic, 3,4,5-trimethoxy-	77	—	170/1.0[k]	62–63[k]	—	—	—	—	—	—	—	Neg.
Piperonylic	89	—	130/0.1	64–66	65.14	65.30	6.83	6.63	6.33	6.38	—	+
Benzoic, *o*-ethoxy-	83	1.5160	115/0.1	—	70.55	69.73	8.65	8.64	6.33	6.60	++++	++++
Benzoic, *p*-ethoxy-	90	—	145/2.0	45–46	70.55	70.73	8.65	8.45	6.33	6.26	—	Neg.
Benzoic, *o*-propoxy-	58	1.5145	124/0.5	—	71.45	71.07	9.00	9.08	5.95	6.11	—	Neg.
Benzoic, *o*-isopropoxy-	63	1.5088	114–116/0.5	—	71.45	70.75	9.00	8.92	5.95	6.12	—	Neg.
Benzoic, *o*-bromo	86	1.5490	138–140/2.0	—	51.58	51.74	5.51	5.74	5.47	5.58	+++	++++
Benzoic, *p*-chloro-	86	1.5368	115/0.2	—	62.41	62.53	6.67	6.53	6.62	6.31	—	++++
Benzoic, 2,4-dichloro-	98	—	125–127/0.4[l]	62–64[l]	—	—	—	—	—	—	—	+
Benzoic, 3,4-dichloro-	90	1.5493	192/12	—	53.67	53.07	5.32	5.17	—	—	—	+
Phthalic, monomethyl ester	55	1.5270	136–137/0.5	—	66.36	66.00	7.28	7.27	5.95	6.17	++	—
Phthalic, [*diamide*]	46	—	—	41–42[m]	—	—	—	—	—	—	—	Neg.
o-Toluic, Δ^4-tetrahydro-	83	1.4821	79/0.1	—	73.80	73.87	10.84	10.77	7.17	7.31	—	+++
Cyclohexanecarboxylic	98	1.4720	135/22	—	72.08	71.26	11.55	11.57	7.64	7.67	—	+

Cyclohexanecarboxylic, 1-acetoxy-	90	1.4773	172–177/15	—	64.70	64.83	9.61	9.31	5.80	5.74	—	++++
Cinnamic, *o*-chloro-	68	—	—	87–88	65.68	65.93	6.78	6.63	5.89	5.73	—	Neg.
Cinnamic, *p*-chloro-	84	1.5893	171/1.5	—	65.68	64.96	6.78	6.62	5.89	5.85	—	Neg.
Acetic, bis(*p*-chlorophenyl)-	26	—	—	132[n]	—	—	—	—	—	—	—	Neg.
Chrysanthemumic	82	1.4770	85–86/0.1	—	75.28	74.66	11.28	11.14	6.27	6.58	—	+++
Coumarilic	94	1.5689	135–140/0.3[o]	—	—	—	—	—	—	—	—	Neg.
Fencholic	85	1.4690	103–105/2.0	—	74.61	75.04	12.08	12.04	6.22	6.37	—	Neg.

[a] Mary H. Aldridge of the University of Maryland made the analyses. [b] Based on the acid as starting material. [c] Pitré, *Farm. sci. e tec.* **4,** 657 (1949) [*Chem. Abstr.*, **44,** 4866], reports b.p. 107–108°/16 mm. [d] Maxim, *Bull. Soc. Chem. Romania,* **11,** 29–36 (1929) [*Chem. Abstr.*, **24,** 94], reports b.p. 160°/24 mm. [e] *Ibid.*, b.p. 160°/19 mm. [f] *Ibid.*, b.p. 163°/17 mm. [g] Couturier, *Ann. chim.*, **10** [11] 569 (1938), reports m.p. 83–84°. [h] *Ibid.*, p. 568, m.p. 118°. [i] *Ibid.*, p. 577, b.p. 170°/17 mm., m.p.35°. [j] *Ibid.*, p. 178, b.p. 148°/4 mm., m.p. 45°. [k] *Ibid.*, p. 579, b.p. 210°/4 mm., m.p. 54°. [l] Ref. (5) gives b.p. 176–178°/13 mm., m.p. 63–64° [m] Maxim, *Compt. rend.*, **184,** 689 (1927), reports b.p. 204°/10 mm., m.p. 36°. [n] Gokhale, *et al.*, *J. Univ. Bombay,* **16,** No. 5, 32 (1948) [*Chem. Abstr.* **43,** 1144], report m.p. 138°. [o] Papa *et al.*, *J. Am. Chem. Soc.*, **72,** 3885 (1950), report b.p. 157–159°/4 mm.

REFERENCES

(1) DRAIZE, ALVAREZ, AND WHITESALL, *J. Pharmacol. Exptl. Therap.*, **93**, 26 (1948).
(2) TRAVIS, MORTON, JONES, AND ROBINSON, *J. Econ. Entomol.*, **42**, 686 (1949); MORTON, TRAVIS, LINDUSKA, *U. S. Bur. Ent. and Plant Quar. E-733*, p. 10–11 (1947); SMITH AND BURNETT, *J. Econ. Ent.*, **42**, 439 (1949).
(3) BARTHEL, LEON, AND HALL, *J. Org. Chem.*, **19**, preceding article (1954).
(4) DRAKE, SHENK, AND EAKER, U. S. Patent 2,627,487 (1953).
(5) MARTIN, MARGOT, NERACHER, SCHINDLER, AND HODEL, U. S. Patent 2,551,891 (1951).
(6) McCABE, U. S. Patent applied for, Serial No. 339,188 (1953).
(7) GERTLER, U. S. Patent 2,408,389 (1946).
(8) DRAKE, EAKER, MELAMED, SHENK, AND WEAVER, O.S.R.D. Report No. 6370 (1945).
(9) DRAKE, EAKER, AND SHENK, *J. Am. Chem. Soc.*, **70**, 677 (1948).