Rodent Repellency of Some Substituted Phthalimides

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Twenty-eight substituted phthalimides were either synthesized or procured, tested for rat repellency, and their indices of repellency computed. The data obtained were analyzed with the objective of correlating rat repellency with chemical structure and configuration. Although the results do not afford the postulation of a precise correlation, they do suggest that such a correlation exists.

THE FISH AND WILDLIFE SERVICE has long shown an interest in chemical substances which will deter or inhibit rodent attack upon packaged commodities. Tests upon more than 6500 compounds have shown that repellent activity may be correlated with composition and molecular configuration. Hydrocarbons, carboxy acids, ethers, alcohols, and esters have little repellency; but activity may be increased by introduction of nitrogen as a ring constituent or in substituent amido, amino, or nitro groups. Among the series of compounds showing promise in this respect, the *N*-substituted phthalimides are particularly interesting. Bellack and DeWitt (1) have reported the preparation and testing of 14 of these compounds along with several other groups of cyclic imides. The activity of some members of this series indicated that a more complete study of these compounds was advisable; therefore, a number of phthalimides containing substituents both on the imino nitrogen and at various positions in the benzene nucleus were synthesized or procured from cooperating agencies and industries. These compounds were screened according to the procedure of DeWitt *et al.* (2) and the repellency indices computed and tabulated.

Since investigations at this agency often have indicated that the addition of a nitro group to an aromatic nucleus tends to accentuate repellent activity, the decision was reached to prepare 3-nitro analogs of eight of the phthalimides previously studied.

PREPARATION OF COMPOUNDS

The compounds in Table I and half of those in Table II were prepared in laboratories of the Fish and Wildlife Service, Laurel, Md. *N*-(2-Bromoethyl)-phthalimide and its 3-nitro and 4-nitro analogs were prepared by Gabriel's synthesis as described by Weygand (3). The other imides were prepared by heating the amine with phthalic anhydride or phthalic acid to form the amine salt. This reaction product was then heated under reduced pressure to approximately 150° for varying periods of time in the manner reported by Bogert and Boroschek (4). *N*-(3-Cyanopropyl)-phthalimide was prepared in this fashion and converted to *N*-(3-carboxypropyl)-phthalimide through alkaline hydrolysis by the method described by Vogel (5). All synthesized compounds were recrystallized, usually from absolute alcohol or from alcohol containing 1–10% by weight of water, to a constant melting point. These melting points compared favorably with those given in the literature. These compounds were soluble in acetone, a little less soluble in alcohol, and very slightly soluble in water. Melting points for synthesized compounds are indicated. Compounds submitted by cooperating agencies were tested as received without purification.

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REPELLENCY TESTS

Individually caged laboratory rats weighing between 150 and 250 Gm. were given a choice of two food containers, one containing 20 Gm. of ground laboratory food and the other a 2% mixture of the test compound in the same food. Daily food consumption was determined through the 4-day test period. By substituting the data in the Bellack-DeWitt formula

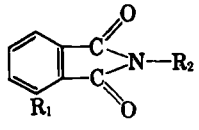
$$K = 100 - 1/100W \times (8T_1 + 4T_2 + 2T_3 + T_4) \times (U_1 + U_2 + 2U_3 + 4U_4 + 8X)$$

where W represents the body weight of the test animal in kilograms, $T_1 - T_4$ are grams of treated food consumed on the respective days, $U_1 - U_4$ are grams of untreated food consumed the respective days, and X represents grams of untreated food remaining at the end of the test period, the repellency indices (K) were computed. K values of 85 or higher indicated sufficient repellency to warrant more exhaustive investigation, such as barrier tests or simulated warehouse studies. Compounds showing indices of less than 85, but approaching it, often suggested other compounds of possible merit as repellents.

RESULTS AND DISCUSSION

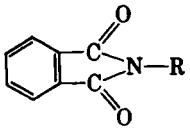
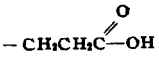
Results from the preparation and testing of 3-nitro analogs of previously studied phthalimides are given in Table I. The findings indicate that when the carbon chain of the *N*-substituent exceeded three carbon atoms, the compound containing the 3-nitro substituent was less repellent than the corresponding compound with an unsubstituted benzene nucleus. When the carbon chain was three carbon atoms or less in length, the converse was true. *N*-Bromoethyl-phthalimide gave a K value of 84, which was intermediate between that of the

TABLE I.—RELATIVE REPELLENCIES OF *N*-SUBSTITUTED PHTHALIMIDES AND 3-NITRO-*N*-SUBSTITUTED PHTHALIMIDES



R_2	Repellency Index, K $R_1 = H_1$	Repellency Index, K $R_1 = NO_2$	M.p., °C. $R_1 = NO_2$
CH_3	62.5	72	111
C_2H_5	53.8	87	104
C_3H_7	71.4	93	84
i—C_3H_7	77.2	81	92
i—C_4H_9	97.3	55	76
C_5H_{11}	95.4	93	74
C_6H_{13}	90.4	49	68
C_8H_{17}	64.6	59	71

TABLE II.—RAT REPELLENCY INDICES AND MELTING POINTS OF SUBSTITUTED PHTHALIMIDES

R	*K* Value	M.p., °C.
Part One		
		
	83	82
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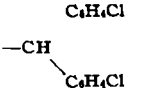
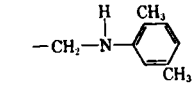
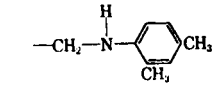
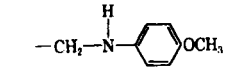
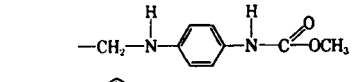
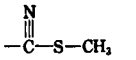
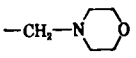
	65	
	70	
	88	
	71	
	74	
	77	169
	91	138
	91	
	69	
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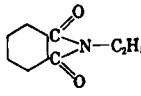
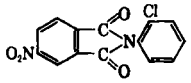
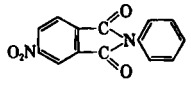
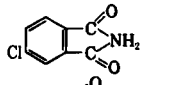
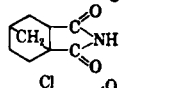
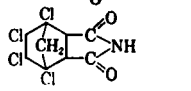
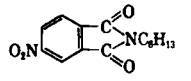
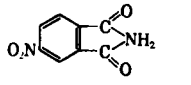
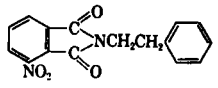
	89	
	99	61
	87	69
	89	
	96	
	61	
	58	
	87	
	66	83

3-nitro analog [96] and the 4-nitro analog [82]. *N*-Butyl phythalimide and *N*-butyl-3-nitrophthalimide exhibited approximately the same repellency, 100 and 99, respectively.

Consideration of the compounds will indicate effects of changes in structure on the index of repellency. For example, *N*-(*o*-chlorobenzyl)-4-nitrophthalimide is decidedly more repellent than the corresponding *p*-chloro isomer. It is also evident that *N*-[2-(3-methyl-pyridyl)]-phthalimide is more repellent than *N*-[2-(6-methyl-pyridyl)]-phthalimide. It appears that molecular configuration and especially electronic and spatial phenomena connected with certain highly significant atoms in the molecule give rise to physical properties which cause rats to avoid contact with these substances, even though they have a low order of toxicity. The exact nature of these phenomena is not understood to the degree that precise predictions of repellency from structure may be attempted; but enough general information now is available to enable the investigator to reject, without testing, compounds with little likelihood of repellency. The result has been that the percentage of compounds tested that display appreciable repellency has increased decisively.

Data obtained from these studies suggest that a definite and precise relationship between rat repellency and chemical structure will eventually be determined, but that this relationship is complex and involves many factors which are not readily discernible. These data serve to support the contentions of Bellack and DeWitt that certain substituents tend to reduce the repellent activity of other substituents in given basic molecular structure. These results further suggest that a substituent which will enhance repellency when attached to one molecule may inhibit repellency when attached to another; *N*-(2-bromoethyl)-phthalimide is more repellent than *N*-(2-bromoethyl)-4-nitrophthalimide, while phthalimide ($K=18$) is much less repellent than 4-nitrophthalimide ($K=87$). Findings also support the idea that the lengthening of an aliphatic hydrocarbon chain of an *N*-substituent beyond four carbon atoms causes a diminution rather than an increase in repellent effect.

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