Correlation between Chemical Structure and Rodent Repellency of Benzoic Acid Derivatives

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Sixty-five benzoic acid derivatives were either prepared or obtained from commercial concerns, tested for rat repellency, and their indices of repellency computed. The data from these tests were considered analytically for any correlation between chemical structure and rat repellency. The results suggest a qualitative relationship which is useful in deciding probability of repellency in other compounds.

THE importance or necessity of adequate procedures for the prevention of economic damage by rodents is universally recognized. Various methods have been employed for this purpose, including rodentproofing of buildings and the use of toxic agents. Although methods designed to eliminate rodent infestations are the most desirable, it is sometimes impossible or impractical to utilize such procedures for the protection of materials in temporary storage dumps. In such cases, the incorporation of a chemical repellent in a physical barrier—e.g., boxboard, plastics, or other packaging materials—might prove highly advantageous.

Chemicals for this purpose should be nontoxic, free from objectionable odors and tastes, and capable of application in such manner that they do not contaminate the packaged articles. Packaging costs must remain commensurate with the value of articles to be protected, and the chemical must be suitable for application under conditions and by procedures normally followed in the manufacture of packaging materials. The Bureau of Sport Fisheries and Wildlife has screened more than 7000 compounds in the search for materials meeting these requirements, and has shown that repellent activity may be associated with certain functional groups or configurations (*2–4*). Extension of the test procedures to derivatives of benzoic acid has furnished additional data on these relationships.

Experimental Methods

Bioassay Procedure. The materials were tested by a method described in a previous publication (*2*). Individually caged laboratory rats were given two food cups, one containing 20 grams of a standard laboratory diet, and the other containing similar food plus 40 mg. of test material. Water was supplied *ad libitum*, and food consumption was determined daily during the test period of 4 days. At the close of the experiment, the degree of repellency of the test material, expressed as the index number, K, was calculated by the formula:

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

where W equals the body weight of the animal (in kilograms), $T_1 \ldots T_4$ represent the consumption (in grams) of the treated food on the first through the fourth day of the test, $U_1 \ldots U_4$ represent the consumption of the untreated food, and X represents the residue of untreated food at the conclusion of the experiment. The calculation of K was based on the assumptions that, in the absence of repellent activity, all food would be consumed by the end of the third day and that any abnormality in rate of food consumption or differentials in the rates of acceptance of treated and untreated foods would be due to the effects of the test compound. Materials with a K value of 85 or higher were reserved for further study, while those with lower values were not considered to offer promise as rodent repellents.

Results and Discussion

In the investigation here reported benzoic acid and various derivatives of benzoic acid were tested for repellency as described above. The repellency indices are recorded in Table I. Benzoic acid was found to be nonrepellent. Tests on 300 other carboxy acids indicate that there is no repellency connected with the carboxyl group itself, yet the carboxyl group when associated with other groups often resulted in compounds of high repellency (compounds 1 to 6). These compounds contain hydroxyl groups in the 2 position and electron-releasing groups in the 5 position with respect to the carboxyl group. Organic acids without these characteristics showed no repellency. Addition of other substituents tended to reduce rather than enhance the repellent quality.

Hydrazides were invariably repellent, some much more so than others, as is shown in compounds 7 to 11.

Benzamide derivatives (compounds 12 to 19) in which the aromatic nucleus is substituted were relatively ineffective, except for the 4-nitro compound, but when alkyl substituents were placed on the nitrogen atom (compounds 20 to 30) repellency increased spectacularly, producing some of the better repellents uncovered during the investigations. Repellency seemed to increase with increasing complexity of the alkyl substituent. Halogen, alkyl, and methoxy substituents on benzanilide in the main were poor repellents (compounds 31 to 65) but with several glaring exceptions, showing again the specificity asserted by Ferguson and Lawrence (*5, 9*). *N*-alkyl nitrobenzamides were repellents; *N*-aryl nitrobenzamides were invariably poor repellents, sometimes having negative repellency indices (compounds 31, 62 to 64)—the rats ate the supposed repellent in preference to their regular food.

Geldard (*8*) has shown that the chemical and physiological nature of the tongue in all higher animals is such that even a very slight change in chemical structure will drastically alter the effect of that chemical on the taste buds and may shift the taste sensation from bitter to tasteless to sweet or vice versa. Admittedly, the sense of taste is not uniform as one moves from one species to another. That which is pleasant to a rabbit may be intolerable to a rat. Sodium chloride stimulates a salty response in the rat but not in the cat or the rabbit, while potassium chloride reverses the sensation order. This phenomenon is actually one of neural response rather than specific taste sensation, but it appears that the variation between neural response and taste sensation should be to some measure concomitant. With any species a slight change in an organic molecule may cause a radical change in the taste of the substance. One may consider the difference between the taste of fructose and of glucose.

The work of Ferguson and Lawrence (*5*) suggests strongly that the difference between a sweet or pleasant taste and a bitter or unpleasant one in the human tongue or in that of cat, rabbit, and in-

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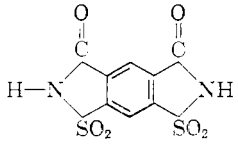
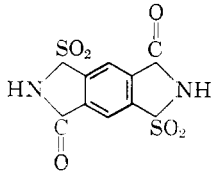
Table I. Repellency Indices of Benzoic Acid Derivatives

	Compound	K Value		Compound	K Value
1	Benzoic acid	17	34	Anisanilide, 2′,5′-dichloro-	−31
2	5,5′-Methylenedi-2,3-cresotic acid	93	35	Anisanilide, 2′-nitro-	92
3	5-Phenylsalicylic acid	100	36	2-Chlorobenzanilide, 2′-chloro-	75
4	5-Bromosalicylic acid	98	37	2-Chlorobenzanilide, 3′-chloro-	59
5	5-Chlorosalicylic acid	100	38	2-Chlorobenzanilide, 4′-chloro-	98
6	3,5-Dichlorosalicylic acid	98	39	2-Chlorobenzanilide, 2′-methyl-	72
7	Benzoic acid, *p*-nitrocyclopentylidene hydrazide	98	40	2-Chlorobenzanilide, 3′-methyl-	64
8	Benzoic acid, *p*-nitrocyclohexylidene hydrazide	98	41	2-Chlorobenzanilide, 4′-methyl-	90
9	Benzoic acid, *p*-nitro(2-ethylbutylidene) hydrazide	94	42	4-Chlorobenzanilide, 2′-methyl-	57
10	Benzoic acid, *p*-nitro(α-methylbenzylidene) hydrazide	86	43	4-Chlorobenzanilide, 4′-methyl-	40
11	Benzoic acid, *p*-nitropiperonylidene hydrazide	70	44	4-Chlorobenzanilide, 3′-chloro-	3
12	Benzamide	22	45	4-Chlorobenzanilide, 2′,5′-dichloro-	35
13	Anisamide	43	46	2,4-Dichlorobenzanilide, 2′-chloro-	32
14	Benzamide, 2-chloro-	69	47	2,4-Dichlorobenzanilide, 3′-chloro-	36
15	Benzamide, 4-chloro-	51	48	2,4-Dichlorobenzanilide, 4′-chloro-	28
16	Benzamide, 2,4-dichloro-	63	49	2,4-Dichlorobenzanilide, 2′,5′-dichloro-	33
17	Benzamide, 3,4-dichloro-	76	50	3,4-Dichlorobenzanilide, 2′-chloro-	17
18	Benzamide, 3-nitro-	68	51	3,4-Dichlorobenzanilide, 3′-chloro-	72
19	Benzamide, 4-nitro-	82	52	3,4-Dichlorobenzanilide, 4′-chloro-	41
20	Benzamide, *N*-octyl-	80	53	3-Nitrobenzamide, *N*-isobutyl-	86
21	Anisamide, *N*-methyl-	74	54	3-Nitrobenzamide, *N*,*N*-diisopropyl-	91
22	Anisamide, *N*-ethyl-	75	55	3-Nitrobenzamide, *N*-cyclohexyl-	74
23	Anisamide, *N*-propyl-	88	56	3-Nitrobenzanilide, 3′-chloro-	56
24	Anisamide, *N*-isopropyl-	96	57	4-Nitrobenzamide, *N*-methyl-	92
25	Anisamide, *N*-allyl-	95	58	4-Nitrobenzamide, *N*-propyl-	92
26	2-Chlorobenzamide, *N*-*sec*-butyl-	93	59	4-Nitrobenzamide, *N*-isobutyl-	84
27	2-Chlorobenzamide, *N*-amyl-	89	60	4-Nitrobenzamide, *N*-sec-butyl-	94
28	4-Chlorobenzamide, *N*-amyl-	90	61	4-Nitrobenzamide, *N*-benzyl-	95
29	4-Chlorobenzamide, *N*,*N*-dipropyl-	95	62	4-Nitrobenzamide, *N*,*N*-bibenzyl-	−2
30	2,4-Dichlorobenzamide, *N*-amyl-	90	63	4-Nitrobenzanilide, 2′-chloro-	−110
31	Anisanilide, 2′-chloro-	21	64	4-Nitrobenzanilide, 3′-chloro-	−10
32	Anisanilide, 3′-chloro-	55	65	4-Nitrobenzanilide, 4′-chloro-	45
33	Anisanilide, 4′-chloro-	59			

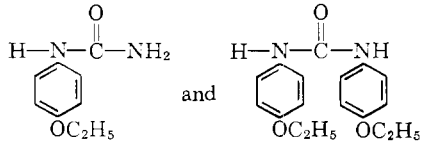
deed the laboratory rat involved only slight variation in molecular structure, in many cases the difference between one geometric isomer and another or even one optical isomer and another—for example, the *d* forms of several amino acids (isoleucine, valine, etc.) are sweet, while the *l* forms are bitter. The compound



is very bitter, while its isomer



is almost tasteless. The tongue easily establishes what an elemental analysis could not. Another example of gustatory specificity is the difference in taste between



and

The monosubstituted urea is very bitter, while the disubstituted material is absolutely tasteless. The pioneering work on the taste of substituted urea was done by Fox (*6*) with the thiocarbamides. Later Ferguson and Lawrence made a thorough study of substituted ureas and found that by addition of a substituent, sweetness could be enhanced, and by addition of another molecule of the same substituent, the taste could be shifted in the other direction, in many cases in a predictable fashion.

Taste sensation has been explained in terms of the effect of the substance on the phenomena which control cell membrane permeability (*10*, *11*), and of chemical structure on solubility within the cell structure of the taste buds (*7*). Beidler (*1*) reduced these relationships to a precise formula from which could be computed the free energy (ΔF) of the reaction between the taste molecule and the taste cell which gives rise to electrical neural activity in the taste nerve. This activity is associated in a not clearly defined manner with the taste sensation. The free energies of sodium salts studied ranged between −1.2 and −1.4 kcal. per mole. These low values suggest that the critical step in taste sensation is physical rather than chemical.

Summary

Variations in rodent repellency of benzoic acid derivatives appear to be direct functions of chemical structure. Slight alteration in the composition or even the geometry of a repellent molecule often significantly changes repellent activity. These changes are in some cases predictable within certain limits, thus rendering unnecessary the testing of many compounds of dubious value.

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Received for review September 19, 1964. Accepted December 21, 1964. Work carried out under grants from the Office of the Quartermaster General.